شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

Introduction

Ciprofloxacin® (CPFX) is a very popular and the most potent fluoroquinolone (FQ). It is active against a broad spectrum of bacteria and has diverse therapeutic prospects ***(Anquetin et al., 2006)***. It is considered as a drug of final resort when all other antibiotics have failed ***(Appelbaum and Hunter, 2000)***.

Currently, the scientific community has significant interest of CPFX® due to its anti-proliferative and apoptotic activities in several cancer cell lines. It can induce time and dose-dependent growth inhibition and apoptosis of various carcinoma, osteosarcoma, and leukemia cell lines ***(Herold et al., 2002)***.

It has been known to have severe side effects as seizures, rhabdomyolysis, tendon rupture, Stevens-Johnson syndrome, interstitial nephritis, and liver injury ***(Zimmerman, 2000; Chalasani et al., 2008)***.

Previous studies reported the undesired effect of CPFX® on salivary glands (SGs) such as significant decrease in total protein and calcium contents ***(Abdollahi and isazadeh, 2001)***. Also, degeneration and disorganization of salivary acini were reported **(*Ibrahim et al., 2004)***. Recently, the use of natural materials in management of medication toxicity has been a growing interest. Cinnamon (CIN) and chia seeds, as an example of natural materials, are demonstrated to have potent antioxidant and anti-inflammatory effects ***(Su et al., 2007; Lee, 2009)***.

Cinnamon is a small tree that grows in India, Sri Lanka, Indonesia, Brazil, Vietnam, and Egypt. It is one of the oldest known spices. The term "cinnamon" refers to its mid-brown color. CIN may serve as potential dietary source of natural antioxidants for improving human nutrition and health ***(Su et al., 2007; Suriyagoda et al., 2021)***.

It has been known from remote antiquity. It was imported to Egypt as early as 2000 B.C. In ancient Egypt, CIN was used to embalm mummies**.** CIN was so highly prized among ancient nations that it was regarded as a gift fit for monarchs and even for a God; a fine inscription records the gift of CIN and cassia to the temple of Apollo at Miletus ***(Bell and Toussaint-Samat, 2009; Burlando et al., 2010)***.

Salvia hispanica L., commonly known as chia, is an oil seed plant that was once used by the Aztecs not only as a foodstuff, but also as an offering to the Gods. Chia seeds began to be used in human food around 3500 B.C. and acquired importance as a staple crop in central Mexico between 1500 and 900 B.C. Chia is an annual plant belonging to the Lamiaceae family, originating in such countries as Guatemala, Mexico and Colombia This seed is a natural source of omega-3 and omega-6 (α-Linolenic acid), fibers (30%), proteins of high biological value, and natural antioxidants that protect the seed against certain adverse conditions ***(Cahill, 2003; Craig, 2004)***. In addition, chia seeds have other important nutritional components such as vitamins and minerals ***(Ayerza and Coates, 2005)***.

They are small, oval-shaped and flat seeds, measured from 2 to 2.5 mm long, 1.2 to 1.5 mm wide, and 0.8 to 1 mm thick. Their color

ranges from dark brown to black, and sometimes gray or white, the white seeds are greater in weight, width and thickness than the darker ones ***(Ixtaina et al., 2008)***.

In modern societies, chia seeds are used and consumed as a source of energy and incorporated into several foods in the diet ***(Ulbricht et al., 2009; Kulczyński et al., 2019)***.

Review of Literature

Major SGs of both humans and rodents consist of three pairs of glands: parotid (PG), submandibular (SMG), and sublingual (SLG) which secrete serous, mucous or mixed saliva through main excretory ducts connecting the secretory units with the oral cavity. A series of discoveries about the salivary ducts in the 17th century by Niels Stensen (1638–1686), Thomas Wharton (1614–1673), and Caspar Bartholin (1655–1738) established the fact of exocrine secretion of the SGs ***(Amano et al., 2012)***.

The total volume of saliva produced each day in human adult SG is 500 to 1500 ml. The total saliva consists mainly of the different glands' secretions; SMG (65%), PG (23%), SLG (4%) and minor SGs (8%) ***(Sreebny and Vissink, 2010)***. The salivary flow and composition are related to the state of SGs. Therefore, any alteration of the integrity and activity of SGs can change saliva flow and composition ***(de Almeida et al., 2008; Mravak-Stipetic, 2012)***.

- Anatomy of SMG:

Submandibular SG is approximately half the size of PG in humans, but it is the largest one of the three major SGs in rats ***(Treuting and Dintzis, 2011)***.

In humans, the SMG is located in superior space of the mylohyoid muscle of the neck, inferior to the mandible, superior to the hyoid, and

posterior to the anterior belly of the digastric muscle. it divided into two main parts: a large superficial portion located between the mandible and mylohyoid muscle and a smaller deep portion located in the sublingual facial space, while in rats; SMG is located in the ventral cervical subcutaneous region in the anterior neck spaces between the submandibular lymph nodes and the sternum ***(Treuting and Dintzis, 2011; Ellis, 2012; Hemmat et al., 2017; Markey et al., 2018)***.

The SMGs and SLGs are separate structures in humans but fused in rats encapsulated with a common fascia ***(Jonjic, 2001, Amano et al., 2012)***.

- Physiology of SMG:

Saliva secretion in both humans and rats is controlled by both parasympathetic and sympathetic innervation of the autonomic nervous system ***(Anderson and Garrett, 1998)***.

Parasympathetic innervation in SMG for both rats and humans starts with stimulation from the superior salivatory nucleus via chorda tympani branch of the facial nerve, propagates along SMG ganglion and finally innervates the gland via postganglionic fibers ***(Garant, 2003)***.

Sympathetic stimulation of the SMG starts in the first and second thoracic segments of the spinal cord. In this region, nerve fibers coalesce in the superior cervical sympathetic ganglion and then connect to post-ganglionic fibers then traveled along the maxillary artery and through the submaxillary ganglion to the SMG ***(Garant, 2003)***.

When sympathetic fibers traveled to the gland, the neurotransmitter norepinephrine activates both α-adrenergic and β-adrenergic receptors, which in turn leads to protein secretion ***(Maruyama et al., 2018)***.

In rats, SMG receives blood supply from the lingual and maxillary branches of the external carotid artery with blood returning to the heart through the anterior facial vein. Likewise, human SMG receives blood supply from the lingual and facial arteries that branch off the external carotid artery. The returning blood drains through the small facial vein branches that coalesce to form the facial vein prior to joining the internal jugular vein ***(Holsinger and Bui, 2007; Maruyama et al., 2018)***.

- Histology of SMG:

Each SG consists of two main elements: parenchyma (acini, ducts and myoepithelial cells) and supporting connective tissue (C.T) stroma. From the stroma of the capsule, septa pass to divide the gland into major lobes which are further divided into lobules ***(Holsinger and Bui, 2007)***.

a) Acini.

Acinus is the secretory end piece of SGs that secretes and produces the primitive saliva. An acinus is composed of several secretory cells and surrounded by myoepithelial cells.

The acini provide most of the proteins and fluid of saliva which moisten the oral cavity and initiate digestion by providing digestive enzymes. In addition, it lubricates the teeth, oral mucosa, and food through mucins, modulate the oral flora by peroxidase and histatins and maintain the minerals of the teeth via statherin ***(Tabak, 2006; Redman, 2008)***.

The serous acini consist of 8–12 pyramid-shaped cells, the broad base resting on the basement membrane and the apex faces the lumen. In each cell, the nucleus is rounded and present in the basal part of the cytoplasm also well-developed rough endoplasmic reticulum (RER), a prominent Golgi complex, and round shaped mitochondria are present in the cytoplasm. These cells are arranged in a spherical pattern forming a narrow central lumen. A significant amount of molecular components of serous saliva is found within the secretory granules (zymogen granules) located in the apical cytoplasm. The serous granules had uniformly fine dense contents. They are rounded in shape with definite boundaries ***(Berkovitz et al., 1992; Nanci, 2013; Jeong and Jeong, 2017)***.

Mucous acini are tubule-shaped secretory units. Their secretory cells show basally situated flat nuclei due to large numbers of apically located mucin droplets which have relatively coarse and moderate electrodensity content. Mucous acini also have well developed RER and a prominent Golgi complex, but they have elongated mitochondria compared to those of the serous cells ***(Nanci, 2013; Jeong and Jeong, 2017)***.

Major types of acinar secretory cells are serous and mucous in both human and rodent SGs. However, histochemical and biochemical studies have revealed that the chemical composition and morphological profiles of secretory granules express great diversity between both types of secretory cells ***(Philips et al., 1993)***.

Serous secretory granules contain little glycoconjugates and a large amount of water and ions. In serous acini, the glycoproteins are lightly glycosylated, carry a predominantly neutral charge, and have a molecular weight of less than 100,000 kilodaltons (KD) resulting in watery secretion. On the other hand, mucous secretory granules contain appreciable amounts of mucin and glycoconjugates. Mucous acini produce high molecular weight (1–10 million KD) glycoproteins that are heavily glycosylated with both neutral and acidic sugars resulting in more viscous secretion ***(Redman, 2017)***.

The human SMG is a mixed gland composed of both serous and mucous acinar cells, whereas the rodent one has only the serous type ***(Amano et al., 2012)***.

In both human and rodent SGs, the serous cells are correctly termed ‘seromucous’ as the serous granules contain moderate amount of glycoconjugates and produce a mucin of 100,000 KD ***(Redman, 2017)***.

b) Ducts.

The duct system is formed of a highly branched ductal network and composed of three different types of ducts known as intercalated, striated and excretory ducts ***(Nanci, 2013)***.

i. Intercalated Ducts.

Intercalated ducts (IDs) connect acini with larger ducts. It is important for salivary gland homeostasis and replenishment, it is considered as salivary gland pluripotent stem cells that give rise to acinar, myoepithelial and ductal cells ***(Ellis and Auclair, 2008)***.

The IDs of SMG are shorter compared to those of PG. They are lined with cuboidal cells with central rounded nuclei and prominent nucleoli. In cross sections, they have a smaller diameter than acini and other ducts.They have well defined Golgi complex, large number of ribosomes and less developed RER ***(Nanci, 2013; Omar et al., 2017)***.

Granular intercalated duct (GID) is present in the IDs of female rats. It is lined by cuboidal cells possess secretory granules. The cytoplasm is stained intensely eosinophilic. The nucleus is oval, basophilic and slightly shifted to the basal part of the cell. In addition, multiple dark secretory granules are present apically. The lumen of GID is larger than that of the conventional ID ***(Kotyk et al., 2014)***.

ii. Granular convoluted tubules.

The granular ducts (granular convoluted tubules, GCTs) are located between the IDs and SDs in the rodent SMGs. The duct wall is composed of a simple columnar epithelium. However, the principal cell type of the GCTs is high-columnar secretory cells. The apical region of this cell is filled with rounded uniformly dense secretory granules. These secretory granules secrete and store proteases and bioactive peptides such as epidermal, fibroblast, insulin-like, and nerve growth factors (EGF, FGF, I-LGF, NGF respectively).The luminal surface is usually straight, but may bear sparse short microvilli. The major portion of the cell's organelles lies in the basal half to third of the cell (granule-free zone). The cells possess; a pale round nucleus with finely dispersed chromatin and a distinct nucleolus, abundant RER with widely dilated cisternae**,** mitochondria and Golgi complexwhich is located apical to the nucleus ***(Gresik, 1994; Nagy et al., 2001; Amano et al., 2012)***.

Rodents display sexual dimorphism in their SMGs particularly in the GCTs and GIDs. GCTs are larger and more numerous in the glands of males compared to those of females as they are being androgen-dependent. GID cells are localized in the IDs of female rats SMGs but not in males. On the other hand, human SMGs have neither GID nor GCTs and do not display any sexual dimorphism ***(Pinkstaff, 1998; Nagy et al., 2001; Kurabuchi, 2002)***.

In addition, "pillar cells" with a narrow luminal surface and wide base exist sandwiched between principal GCTs cells. They are non-

granulated cells with minimal amounts of RER and Golgi apparatus in a cytosol of increased electron density. Their apical cytoplasm usually contains many small electron-lucent vesicles. These cells often are narrow, lack basal infoldings, and have relatively abundant microvilli. The functional roles of these pillar cells are unclear, but a paracrine function based on FGF2 immunolocalization in their cytoplasm has been suggested. It is strongly positive to S100 protein which acts as calcium intercellular signaling protein involved in the discharge of granules in the GCT ***(Amano et al., 1993; Gresik, 1994; Mori et al., 2011)***.

iii. Striated Ducts.

The striated ducts (SDs) are composed of a single layer of tall columnar cells with rounded centrally located nuclei and eosinophilic cytoplasm. The cells have deeply infolded basal membranes accompanied by the longitudinally arranged, numerous, dark and elongated mitochondria with clear cristae. RER is absent or poorly-developed and free ribosomes are rare. The plasma membranes of adjacent cells are held together by junctional complexes close to the lumen and by desmosomes concentrated mainly along the borders in the apical halves of the cells. By light microscopy (LM), the vertically arranged mitochondria appear as eosinophilic striations or radial lines, based on which, these ducts are named. These ducts are more branched and extensive in SMG than other SGs ***(Tandler, 1987; Nanci, 2013; Kotyk et al., 2014)***.

The principal function of the striated ducts is the regulation of secretion and reabsorption of electrolytes via a bi-directional transport between the lumen and the ductal cells, promoting the essential salivary modification from isotonic to hypotonic saliva, in which sodium ions (Na^+) and chloride ions (Cl^-) are reabsorbed, while bicarbonate ions ($HCO3^-$) and potassium ions (K^+) are transported to the lumen using the Na-K pump and the Cl-HCO_3 pump ***(Varga, 2012; Nanci, 2013)***.

iv. Excretory Ducts.

Excretory ducts (EDs) follow SDs and connect the glandular lobules and lobes to the oral cavity through the main excretory duct. The SDs join each other to form larger intralobular ducts. These ducts gradually increase in size and lose the striations to become the excretory interlobular duct. They are responsible for continuing the reabsorption of Na^+ and Cl^- as well as secretion of K^+ and $HCO3^-$ and then conducting the final saliva to the oral cavity. The epithelium of the excretory duct consists of pseudostratified columnar epithelium cells. In larger ducts occasional goblet cells and ciliated cells may be seen. The ductal epithelium of the main excretory duct slowly undergoes a transition to cuboidal epithelium, stratified epithelium and finally into stratified squamous epithelium when it merges with the epithelium of the oral cavity ***(Nanci, 2013; Bavle, 2015; Redman, 2017)***.

c) Myoepithelial cells (Basket cells).

These cells are shaped like starfish and situated between the basal lamina and the acini as well as IDs but not SDs or EDs in both human