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The effect of Ashwagandha Versus Amitriptyline on the Histological Structure of Submandibular Glands in Albino Rats

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BACKGROUND: Amitriptyline has a lengthy track record of success in treating depression. It is used less frequently due to its extensive side-effects including anticholinergic side effects, oxidative stress and high toxicity in over dose. Ashwagandha is an essential ancient herb having anti-depressant, antioxidant properties. **Aim of study:** To evaluate the histological effects of Ashwagandha& Amitriptyline on the salivary glands in rats. **Material and Methods:** forty healthy albino rats that were 8-10 weeks old and weighed 200-250 g were apportioned into four groups randomly. Group I (Control) received distilled water for 30 days. Group II received amitriptyline (10mg/kg) orally. Group III was given ashwagandha root extract (200mg/kg) orally and Group IV was given a combination of amitriptyline (10mg/kg) orally and ashwagandha root extract (200mg/kg) orally for 30 days. Rats were euthanized at the end of 30 days. Submandibular glands were dissected, stained with hematoxylin & Eosin and examined histologically. **Results:** The Histological examination of the submandibular glands tissue showed that, group II exhibited eosinophilia, atrophy and necrosis of the cells and congested blood vessels. Group III exhibited a normal architectural picture. Group IV exhibited necrosis and degradation of epithelial cells lining granular convoluted tubules, atrophy in acini lobules and congestion of blood vessels. **Conclusion:** Amitriptyline induced degeneration of Submandibular glands in rats after 30 days of treatment. Ashwagandha alone has protective effects on salivary glands. But, Ashwagandha will interact with Amitriptyline causing further degeneration of Submandibular glands as a result of the Fenton reaction**.**

Keywords: Amitriptyline, Antioxidants, Ashwagandha, Depression, Submandibular glands.

Introduction

Depression is a mood disorder that causes a persistent feelings of loss of interest and sadness [1]. Emptiness, sadness and irritated moods are regular components of depressive disorders and they are accompanied by changes in the body as the mind that have a major influence on the individual's capability to take delight in routine activities, alterations in sleeping habits and appetite, loss of power, and suicidal ideas [2]. Nearly, 60% of depressed persons do not seek medical care due to erroneous assumptions. Many people think the stigma surrounding mental illness is undesirable in society and that it can negatively impact both personal and professional life. Although the majority of antidepressants are proven to be effective, each person's response to medicine may vary [3]. Depression may result from both hereditary and environmental factors and it is three times more frequent in first-degree relatives of depressed persons than in the general population[4].The symptoms of depression can be treated with medications and brief psychotherapy(cognitive-behavioral therapy, interpersonal therapy). Combination therapy has also been associated with noticeably higher rates of depressive symptom reduction, enhanced

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quality of life, and improved treatment compliance [5]. The potential of Cognitive-behavioral therapy to prevent relapse is also supported by research [6]. Tricyclic antidepressants (TCAs) like Amitriptyline have a lengthy track record of success in treating depression, but It is used less frequently due to its extensive side-effects and high toxicity in overdose [7]. Ashwagandha according to number of studies has antidepressant, anti parkinsonian, anxiolytic, antioxidant and anticarcinogenic properties, it is known as Indian ginseng and Indian Winter Cherry which is an essential ancient herb whose roots have been used in Ayurveda and Unani medicine in India for centuries [8]. The root smells like a horse therefore, it is named the Indian name «Ashwagandha» while the meaning of the Latin word «somnifera» is sleep inducer referring to its pharmacological stress releasing effect [9]. Alkaloids and steroidal lactones are responsible for the root's pharmacological action [10]. This research compared the histological alterations caused by ashwagandha and amitriptyline on the salivary glands of rats.

Materials and Methods

Animals

This research used forty healthy albino rats that were 8-10 weeks old and weighed 200-250g.They were obtained from the Faculty of Veterinary Animal House at Mosul University, Iraq. The animals were kept at a room temperature of 222±C° with12 hours of light and darkness, unrestricted access to food and water *add libitum*. All procedures followed the guidelines of the Faculty of Dentistry's institutional animal research ethics committee in the College of Dentistry, University of Mosul, Iraq (UOM. Dent/ A.L.56/22).

Experimental substances

Ashwagandha root extract was available in the form of powder obtained from Naturalaya Kimya company/Antalya /Turkey Fresh solution of Ashwagandha was prepared and administered orally every day.

Amitriptyline was available in the form of a tablet from Accord Company, United Kingdom. Fresh solution of Amitriptyline was prepared and administered orally every day.

Experimental design

Forty rats were randomly divided into four groups as following:

Group I (Control, n=10): Rats daily received distilled water at (1.0ml/kg) orally for 30 days using gavage needle from the first day to the last day of the experiment.

Group II(Amitriptyline group, n=10):given Amitriptyline 10mg/kg orally[11] daily for 30 days using gavage needle from the first day to the last day of the experiment.

Group III(Ashwagandha group, n=10):given Ashwagandha root extract 200mg/kg orally.[12] daily for 30 days using gavage needle from the first day to the last day of the experiment.

Group IV (combination group, n=10):given a combination of Amitriptyline10mg/kg Ashwagandha root extract 200mg/kg orally for 30 days using gavage needle from the first day to the last day of the experiment.

Specimen collection

All animals in each group were euthenized after 30 days of the administration, two hours after the final treatment, and their salivary glands were removed. For histological analysis, the specimen was put in buffered formalin at a 10% concentration.

Evaluation methods

Histological Techniques

1. Fixation of samples in 10% buffered formalin, followed by water rinsing and dehydration using escalating alcohol concentrations (7% for 24 hours, 80% for one hour, 90% for one hour, and 100% for two exchanges, one hour at a time).
2. The specimens underwent two xylene exchanges, lasting 10 minutes each two
3. The specimens were infiltrated with white paraffin wax and baked at 58°C for two exchanges, lasting two hours each, before being embedded in paraffin wax that was blocked in the tissue cassette.
4. The paraffin block was cut into 4-6 micrometers slices using a rotary microtome, then placed in a circular water bath at 45 degrees Celsius, and finally, an adhesive agent (glycerol with egg albumin in a volume of one volume) was used.
5. The slide is immersed in xylene, cooked in an oven at 56 degrees Celsius for 45 to 60 minutes, and then placed in the second change of xylene for five minutes.
6. Rehydration: Absolute alcohols gradually rehydrated the area (100 percent) 90 percent and 70 percent of alcohol are consumed after two exchanges of two minutes each.
7. Placed in distilled water for 5 minutes.
8. Staining with hematoxylin and eosin:

Sections were submerged in a glass staining jar filled with hematoxylin for five minutes, after which they were placed in the jar with eosin for one minute after being immersed in tap water.

9. Dehydration through two minutes of escalating alcohol concentration (95 percent for two minutes, then 100 percent for two minutes each).
10. Xylene was used for two exchanges of two minutes each to clear the area.
11. The segment was coated with a coverslip using D.P.X. as a mounting agent after the slide had been stained and dried. Histopathological experts examined it under a light microscope.

Results

Histological results

The microscopical examination of the submandibular glands tissue sections referred the presence of changes between groups as shown as following: The control group's rats salivary glands exhibited normal architecture, with granular, convoluted tubules, mucous and serous acini and striated ducts (Fig. 1 and 2).

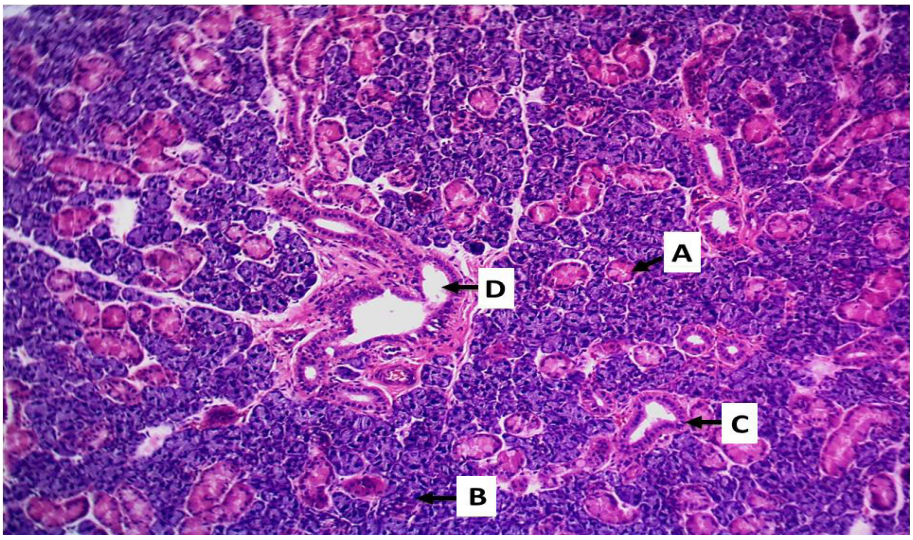

Fig. 1. Photomicrograph of rat submandibular salivary gland of control group shows normal architecture represented by granular convoluted tubules (A), serous and mucous acini (B), striated ducts (C) and interlobular ducts (D). H&E stain, 100X.

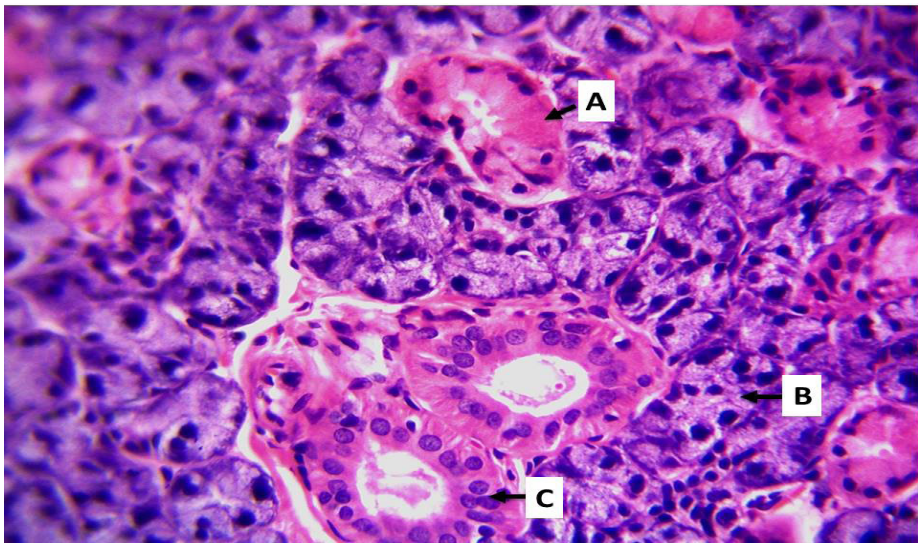

Fig. 2. Photomicrograph of rat submandibular salivary gland of control group shows normal architecture represented by granular convoluted tubules (A), serous and mucous acini (B) and striated ducts (C). H&E stain, 400X.

While Amitriptyline group's rats salivary glands exhibited degeneration and necrosis of epithelial cells lining granular convoluted tubules with atrophy and congested blood vessels (Fig. 3 and 4)**.**

In Ashwagandha group's rats salivary glands exhibited normal architecture representing by granular convoluted tubules, serous and mucous acini, striated ducts and interlobular ducts (Fig. 5 and 6).

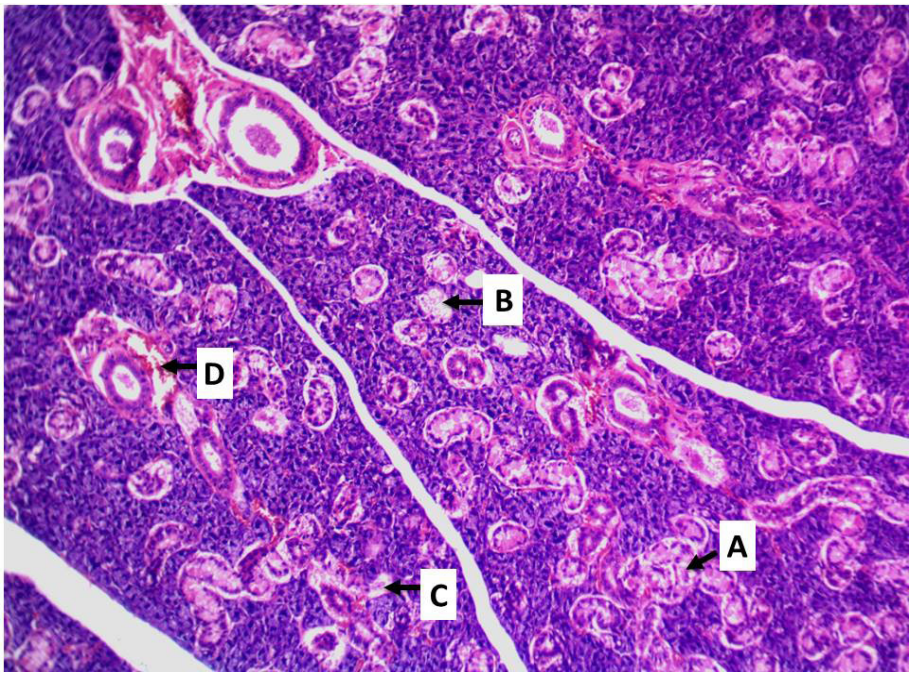

Fig. 3. Photomicrograph of rat submandibular salivary gland of amitriptyline shows degeneration (A) and necrosis (B) epithelial cells lining of granular convoluted tubules with atrophy (C) and congested blood vessel (D). H&E stain,100X.

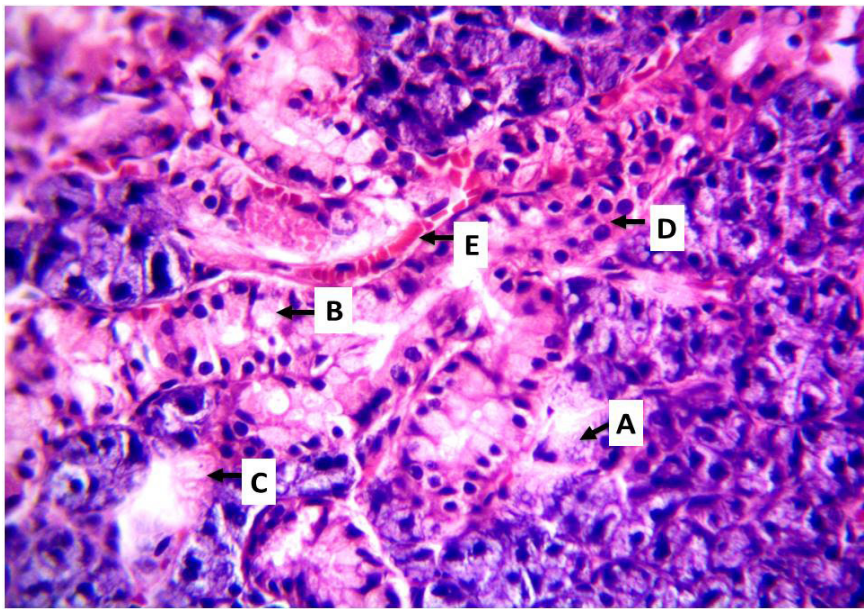

Fig. 4. Photomicrograph of rat submandibular salivary gland of amitriptyline group shows necrosis of epithelial acinar cells (A), degeneration (B) and necrosis (C) of epithelial cells lining granular convoluted tubules (C), presence of inflammatory cells (D) and congested blood vessel (E). H&E stain, 400X.

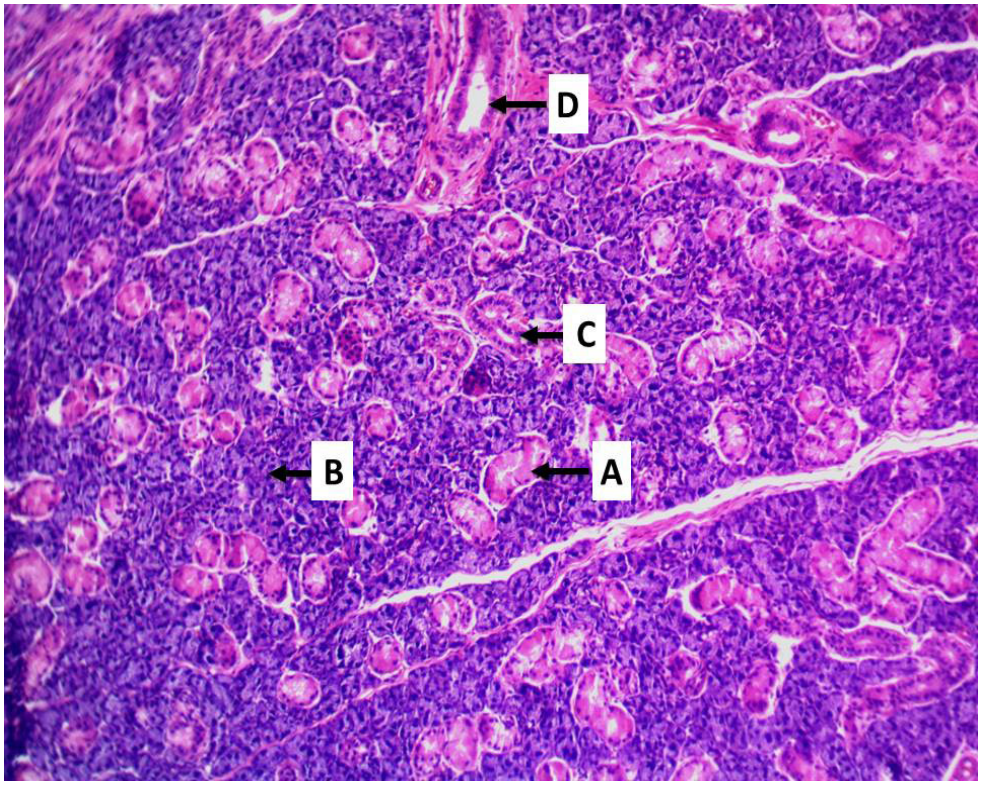

Fig. 5. Photomicrograph of rat submandibular salivary gland of ashwagandha group shows normal architecture representing by granular convoluted tubules (A), serous and mucous acini (B), striated ducts (C) and interlobular ducts (D). H&E stain, 100X.

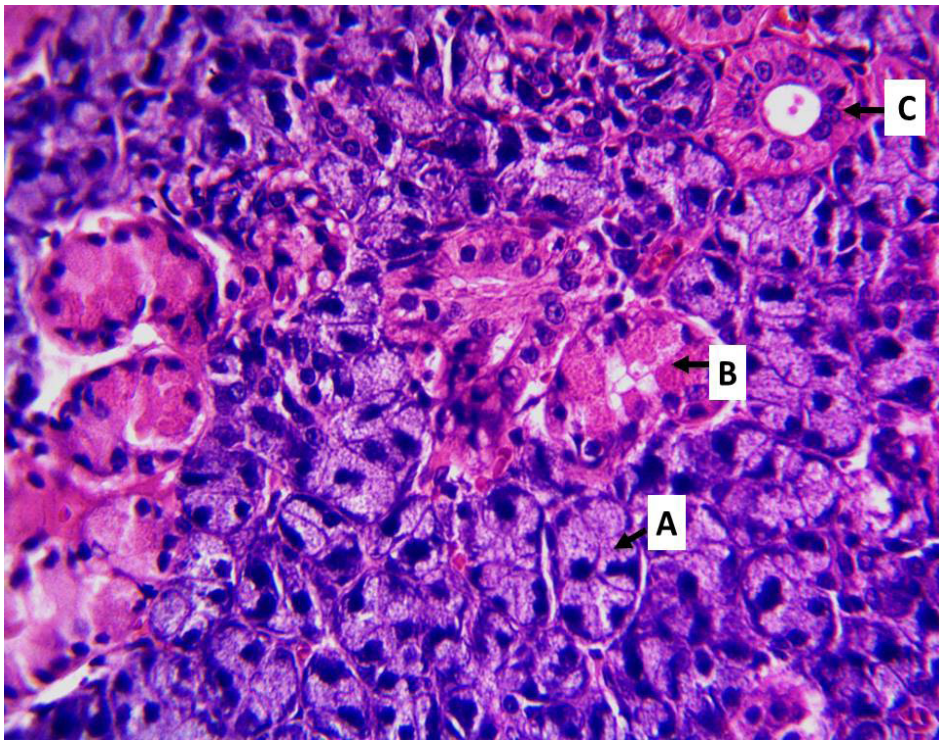

Fig. 6. Photomicrograph of rat submandibular salivary gland of ashwagandha group shows normal architecture representing by granular convoluted tubules (A), serous and mucous acini (B) and striated ducts (C). H&E stain, 400X.

That mean no harmful produce by administration of Ashwagandha .

In the combination Ashwagandha with Amitriptyline we found that combination group's rats salivary glands exhibit necrosis of epithelial acinar cells , degeneration and necrosis of epithelial cells lining granular convoluted tubules , infiltration of inflammatory cells, and congested blood vessels.(Figs.7 and 8).That mean increased oxidative stress when used Ashwagandha with Amitriptyline together .

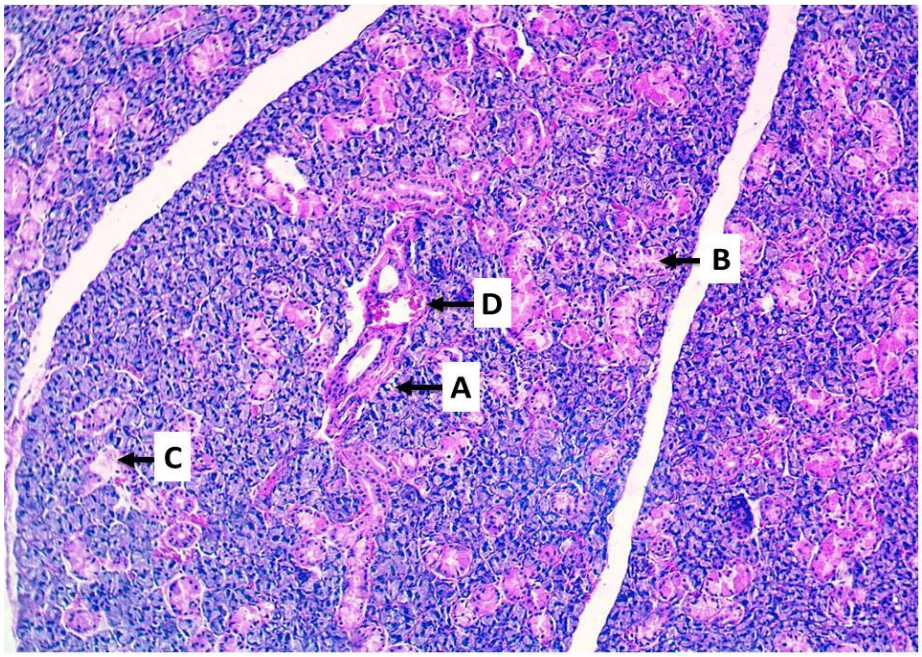

Fig.7. Photomicrograph of rat submandibular salivary gland of combinaion group shows atrophy of acinar cells (A), degeneration (B) and necrosis (C) of epithelial cells lining granular convoluted tubules and congestion of blood vessels (D). H&E stain, 100X.

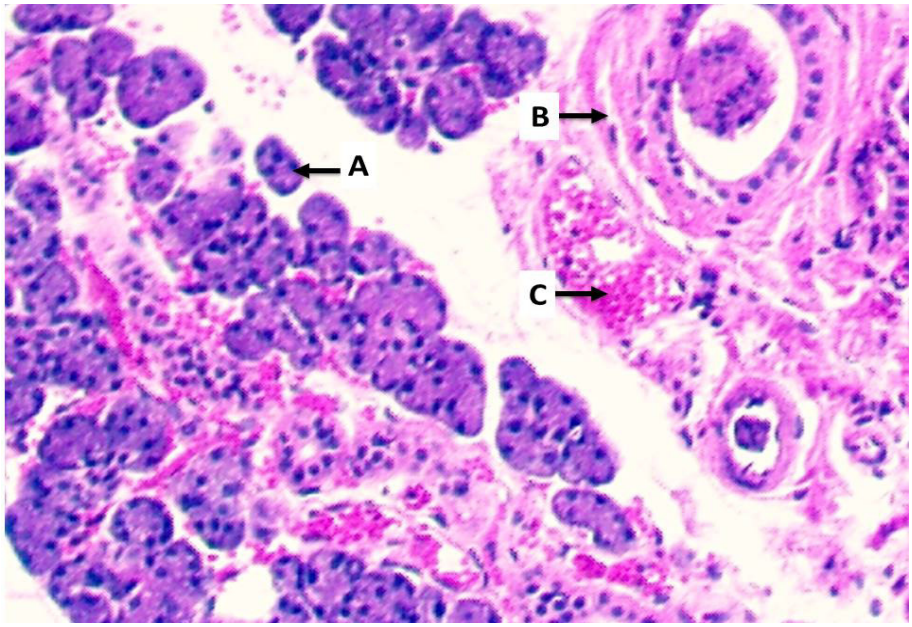

Fig.8. Photomicrograph of rat submandibular salivary gland of combination group shows atrophy of acinar cells (A), Stagnation of secretion and sloughing of epithelium of interlobular duct(B) and congestion of blood vessels(C) . H&E stain, 400X.

Discussion

Depression has long been successfully treated with amitriptyline. Due to their wide side-effect profile, which includes oxidative stress and anticholinergic side effects that cause decrease in salivary glands secretion and effect on oral health. That caused less frequent use of this drug [13] . Therefore, this study used alternative therapy that has antidepressant effect as well as antioxidative activity such as herbal like ashwagandha. This study evaluates the histological effects of amitriptyline, ashwagandha on the salivary glands in rats.

This study found that that administration amitriptyline causes histological effects in salivary glands, Via light microscope, several changes were identified including degeneration and necrosis of epithelial cells lining granular convoluted tubules with atrophy of acini ,infiltration of inflammatory cells and congested blood vessel in salivary glands of rats which were exposed to amitriptyline when compared to those of control by using haematoxylin and eosin stain (H & E). This finding might be attributed to glandular injury and dysfunction [14] . Due to fatty and vacuolar degeneration that may be due to the aggregation of the lipid degenerative products into huge droplets, amitriptyline caused deformity, coalescence, and necrosis of the secretory sections as well as some serous acini being entirely ignored and leaving large vacuoles [15]. Histological changes in this study after giving amitriptyline parallel with other study suggested that amitriptyline administration will induce oxidative stress that is accompanied by significant elevation of malonaldehyde levels and coenzyme Q deficiency[16]. Furthermore offering more proof that amitriptyline-induced oxidative stress occurs in a faulty mitochondrial electron transport chain, decreased metabolic oxygen consumption, ATP depletion, and low energy metabolism is a study by Bandegi et al. [17].

Mitochondria themselves are considered the main source of cellular energy and reactive oxygen species production [18]. Byproducts of electron leakage from mitochondrial respiratory chain complexes I and III include superoxide anions and hydrogen peroxide, which are both referred to as mitochondrial reactive oxygen species [19] .These species are eliminated by the cellular antioxidant defense system, which is made up of superoxide dismutase, catalase, and glutathione peroxidase, these species are harmful to cells' mitochondria [20]. However, due to their proximity to the source of free radical formation, high amount of polyunsaturated fatty acids, and lack of mitochondrial DNA histones, mitochondrial membranes and DNA are particularly vulnerable to oxidative damage[21] . The oxidative stress is always associated with mitochondrial dysfunction as a result of blockage of electron transport chain causing accumulation of reactive oxygen species, consumption of antioxidants and accumulation of cytotoxic mediators [22]. In order to denote the positive feedback effect of ROS in driving their further synthesis in mitochondria, Zorov et al. suggested the phrase "ROS-induced ROS release." It is currently believed that this continuous cycle of ROS formation, forms part of the pathology of diseases caused by ROS [23].

In this study, amitriptyline administration caused histopathological changes in the salivary glands. This effect may be related to the drug's effect on mitochondria, which can result in dysfunction due to oxidative damage represented by morphological changes and functional losses of mitochondria, The permeabilization caused by oxidative stress to the mitochondria can start the mitochondrial apoptotic process. Particularly, release of cytochrome C from mitochondria to the cytoplasm is caused by opening of the mitochondrial permeability transition pore (mPTP), which in turn activates pro-apoptotic caspases (Enzyme for apoptosis)[24-25]. And through activation of p53 protein and other transcriptional factors, that is agrees with apoptosis and atrophy of cells of salivary glands seen in this study in group treated with amitriptyline manifested by degeneration and necrosis of epithelial cells lining granular convoluted tubules with atrophy in salivary gland [26].

Alterations in calcium homeostasis and mitochondrial DNA mutation are frequently followed by mitochondrial malfunction [25]. The formation of reactive oxygen species was reported as a crucial stage in the elicitation of apoptosis immediately before loss of mitochondrial membrane potential, hence the most prevalent mechanisms responsible for starting apoptosis after amitriptyline treatment have been presented [27]. Second, after using amitriptyline, a rise in the cytoplasmic calcium level was noted [28]. It has also been noted that amitriptyline causes well-defined regions of coagulative necrosis in the cell, raising the probability that the necrosis was caused by ischemic side effects of these medications [29].

This study shows that amitriptyline administration causes the blood vessels in the salivary gland to congest. This conduction may be related to the oxidative stress that amitriptyline causes, which in turn causes inflammation and endothelial cell damage. This damage results in mitochondrial dysfunction, which in turn causes an amplified oxidative burst and further inflammation[30]. Mitochondrial failure can enhance the expression of pro-inflammatory cytokines and activate the inflammasome through increased free radical generation. The activation of inflammatory mediators and macrophages, can contribute to tissue damage[31].

Antioxidants maintain endothelial cell integrity by preventing mitochondrial malfunction [32] . Like in this study when administration Ashwagandha. The histological examination of salivary glands in ashwagandha group shows normal architecture representing by granular convoluted tubules, serous and mucous acini, striated duct and interlobular duct. Ashwagandha alone will provide protection to the tissue, can be considered a good source of enzymes and non-enzyme antioxidant constituents [33]. Ashwagandha has demonstrated notable anti-inflammatory properties in a variety of illness models, there were no histological alterations in salivary glands in this investigation. Its root extract reduced necrosis, edema, and neutrophil infiltration while exhibiting anti-inflammatory and muco-restorative effects [34]. The cells of the salivary glands in this study were normal following ashwagandha treatment because it was discovered to have a potent inhibitory effect on inflammatory indicators such as cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-a, nitric oxide (NO), and ROS [35]. In accordance with a previous study in human umbilical vein endothelial cells (HUVECs), ashwagandha was found to inhibit phorbol-12-myristate-13-acetate (PMA)-induced endothelial cell protein-C -receptor (EPCR)-induced shedding by inhibiting TNF-a and interleukin (IL)-1b. This study also demonstrated that ashwagandha administration was free from any congestion of blood vessels [36].

In this study ,the histological examination of salivary glands in combination group of amitriptyline and ashwagandha shows degeneration of epithelial acinar cells, degeneration and necrosis of epithelial cells lining granular convoluted tubules, atrophy of acini lobules, increase fibrous tissue between it and congestion of blood vessels that is attributed to the oxidative stress induced by amitriptyline is exacerbated by free radicals produced by iron which is found in enough quantity in ashwagandha[37], to start fenton reaction leading to continuous oxidation reduction reaction represented by oxidizing of Fe(II) to Fe (III) causing free radicals generation and then Fe (III) is reduced to Fe (II) generating further free radicals, So, over production of these free radicals induced by amitriptyline itself and by fenton reaction causes degeneration, necrosis of the epithelial cells lining granular convoluted tubules, atrophy of acini lobules and congestion of blood vessels. this reaction can be explained by the following equation [38].

$$Fe(II) + H_2O_2 = Fe(III) + OH. + H_2O$$

$$Fe(III) + H_2O_2 = Fe(II) + OH_2. + H+$$

$$Fe(III) + OH_2. = Fe(II) + O_2 + H +$$

The harmful hazardous hydroxyl radical is created when hydrogen peroxide, a weak oxidizing agent that crosses cell membranes quickly, interacts with Fe2+[39].

Conclusion

Amitriptyline induce oxidative stress and cause degeneration of salivary glands. Ashwagandha has antioxidant and protective effects on salivary glands when given alone, but, Ashwagandha will interact with Amitriptyline causing further degeneration of salivary glands as a result of Fenton reaction .

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Ethics approval

All procedures followed the guidelines of the Faculty of Dentistry's institutional animal research ethics committee's in the College of Dentistry, University of Mosul, Iraq(UOM. Dent/ A.L.56/22).

Conflicts of interest

The authors declared no competing interests.

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تأثير الأشواغاندا مقارنة بالأميتربتلين على التركيب الهستولوجي للغدد تحت الفك السفلي في الجرذان البيضاء.

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المقدمة: يتمتع ألاميتريبتيلين بسجل حافل من النجاح في علاج الاكتئاب. الا ان استخدامه اصبح بشكل أقل بسبب آثاره الجانبية الواسعة بما في ذلك الآثار الجانبية لمضادات الكولين والإجهاد التأكسدي والسمية العالية في الجرعة الزائدة. الأشواغاندا هي عشبة قديمة لها خصائص مضادة للاكتئاب ومضادة للأكسدة. **هدف الدراسة:** تقييم التأثيرات النسيجية لأشواغاندا وأميتريبتيلين على الغدد اللعابية في الجرذان. **المواد وطرائق العمل**: تم تقسيم أربعين من الجرذان البيضاء الاصحاء والتي يتراوح اعمارها من ٨ إلى ١٠ أسابيع ووزنها ٢٠٠-٢٥٠ غم بشكل عشوائي إلى أربع مجموعات متساوية. المجموعة الأولى (السيطرة) تلقت الماء المقطر فمويا لمدة ٣٠ يومًا. تلقت المجموعة الثانية أميتريبتيلين (١٠ ملغم / كغم) فمويا لمدة ٣٠ يوما. تلقت المجموعة الثالثة مستخلصًا مائيًا من جذورالأشواغاندا بجرعة (٢٠٠ملغم / كغم) عن طريق الفم لمدة ٣٠ يومًا ، وتلقت المجموعة الرابعة مزيجًا من الأميتريبتيلين بجرعة (١٠ ملغم / كغم) عن طريق الفم ومستخلصًا مائيًا من جذورالأشواغاندا بجرعة (٢٠٠ ملغم / كغم) عن طريق الفم لمدة ٣٠ يومًا. تمت التضحية بالجرذان في بعد ٣٠ يوما من العلاج ، وتم تشريح الغدد اللعابية وصبغها بالهيماتوكسيلين والأيوسين وفحصها نسيجيا. **النتائج:** من الناحية النسيجية ، أظهرت المجموعة الثانية فرط الحمضات وضمور الخلايا واحتقان الأوعية الدموية. اظهرت المجموعة الثالثة صورة نسيجية طبيعية . وأظهرت المجموعة الرابعة تنكسًا في الخلايا الطلائية المبطنة للأنابيب الملتفة الحبيبية ،ضمور فصيصات الأسيني ، واحتقان الأوعية الدموية. **الاستنتاجات** : يسبب الأميتريبتيلين تنكس الغدد اللعابية في حين ان اعطاء الاشواغاندا وحدها لها تأثيرات وقائية على الغدد اللعابية. لكن، عند اعطاءهما معا تداخلت الأشواغاندا مع أميتريبتيلين مما تسبب في مزيد من تدهور الغدد اللعابية نتيجة لتفاعل فينتون.

الكلمات المفتاحية: أميتريبتيلين ، مضادات الأكسدة ، أشواغاند ، اكتئاب ، الغدد تحت الفك السفلي اللعابية