The protective effects of *Zingiber officinale* essential oils extract against Atenolol induced adrenal gland in rats (*Rattus norvigicus*)

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Abstract *Zingiber officinale* Roscoe is a perennial herb belonging to the Zingiberaceae family. The chemical compounds were identified by Gas chromatography–mass spectrometry, the results showed that 38 components found in *Z. officinale*, beta-Sesquiphellandrene had the highest percentage was (28.94%), followed by 2- Butanone, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (R)- (16.82%), alpha.-Farnesene (14.45%). The rest of the compounds constituted a smaller percentage, they were represented by Zingiberene, beta.-Phellandrene, Camphene, 1,8-Cineole, Alpha-Cedrene, Elemol, and Shogaol. Histological sections of the adrenal gland treated with atenolol drug showed that the cortex composed of atrophied zona granulosa, vascularized and inflamed zona fasciculate and sever inflammation of zona reticularis, the medulla appear with mild hemorrhage extended between the chromaffin cells, the parenchyma of the medulla consist of loosely, disorganized into clusters and cords resemble the epithelial, the cells large is size, polyhedral shape and appear empty in sections separated by sinusoidal capillaries while the deep layer is zona reticularis formed by pink stained cells and irregular arrangement. While in adrenal gland treated with *Z. officinale* showed more normal histological sections, so that treated with (atenolol and *Z. officinale*) showed mild moderate changes in different adrenal zona, the zona glomerulosa showed normal structure, small cluster beneath the capsule with crowded nuclei, mild hemorrhage area and the cells appeared resemble the lipoblasts.

Keywords: atenolol, adrenal gland, *Zingiber officinale*, essential oil

1. Introduction

Atenolol is a commonly used medicine for arrhythmias, myocardial infarction, hypertension, and angina pectoris (Bankar et al., 1987; Dunn et al., 1997). This approach is also used for the prophylactic treatment of migraines; it was specifically developed to pass through the blood–brain barrier and does not cause adverse effects when given to patients suffering from bronchial asthma and diabetes mellitus. Patient compliance is better with atenolol because it is given once a day and is used to treat dysautonomia, anxiety, and hyperthyroidism (Chrysant et al., 2008; Gunda et al., 2015). Atenolol has a complex effect on the metabolism of fats but not as much as other nonselective betablockers (Heel et al., 1979). In addition to being hydrophilic, relatively lower concentrations of these substances are found in brain tissue (Tripati, 2008).

Medicinal plants can be utilized directly or as a source of chemicals for chemo-pharmaceutical hemisynthesis (Williamson, 2001). Over the past few decades, additional studies have been performed to identify medicinal plants that can be used in conjunction with synthetic medications to reduce adverse effects. *Z. officinale* is one of these plants. Furthermore, medicinal plants can be very effective at preventing the spread of antibiotic resistance, both directly and indirectly through their antibacterial, antiviral, antifungal, and antiparasitic properties and indirectly by reducing antibiotic resistance (Jawad, 1997; Al-Malak, 2004; Al-Saadi *et al* 2017; Castronovo, 2021).

Zingiber officinale Roscoe is a perennial herb that belongs to the Zingiberaceae family and is native to Southeast Asia and the Pacific Islands. The genus consists of 49 genera and 1,300 species (Altman & Marcussen, 2001). Rhizomes are very popular in Asian folk medicine, and their traditional uses are widespread worldwide; they are used mainly as flavoring agents for foods and beverages and as herbal remedies (Blanco et al., 2016; Liu et al., 2019; Zhang et al., 2020). Altman and Marcussen (2001) reported that essential oils are rich in secondary metabolites, including sesquiterpene hydrocarbons and monoterpenoids such as α-zingiberene, ar-curcumene, β-bisabolene, β-sesquiphyllandrene, terpenes, borneol, geranial, camphene, terphineol, geraniol, limonene, β-elemene, zingiberol, and linalool. However, the composition of *Z. officinale* varies according to geographical origin, harvesting and growing conditions, temperature, and processing (Govindarajan, 1982; Al-Hilphy, 2014; Zhang et al., 2017; Al-fekaiki et al., 2017). *Z. officinale* essential oils include phenolic and terpene

compounds, as well as quercetin, β-sesquiphellandrene, zingerone, Zingiberene, gingerenone-A, 6-dehydrogingerdione β-bisabolene, α-farnesene, and α-curcumene (Yeh et al., 2014; Prasad and Tyagi, 2015; Schadich et al., 2016; Ji et al., 2017). Johanson et al. (2021) reported that *Z. officinale* contains Zingiberene, camphene, α-farnesene, sesquiphellandrene, Elemol, [6]-shogaol and α-curcumene. Tarfaouil et al. (2022). There were 43 distinct components in the essential oils of Z. officinale. Zingiberene (22.18%) and 1.8-cinéol (1.8%) were the most prevalent components (43.47%). This compound is very important as an antioxidant and antibacterial agent. E-Citral (19.01%), Z-Citral (14.82%), geranyl acetate (11.90%), geraniol (9.56%), (5.84%), and camphene (4.92%) were identified as the main constituents (Syafri et al., 2022).

Adrenal gland sensitivity to toxic attack is extremely high, and the adrenal gland is reportedly the most common endocrine organ associated with chemically induced lesions (Ribelin, 1984; Harvey, 1999). The adrenal gland has two characteristics that increase susceptibility to toxic assault: it is a discrete gland, and its high vascularity facilitates the delivery of toxins and metabolic substrates as well as the efficient removal of steroid products (Hinson and Raven, 1999). Folic acid and propolis administration in rabbits treated with H_2O_2 and its effect on the adrenal gland were studied previously (Al-Ahmed et al., 2021). The purpose of this study was to assess the preventive effects of ginger (*Zingiber officinale*) against adrenal toxicity caused by the drug Atenolol.

2. Materials and Methods

2.1. Collection and preparation of powders

Z. officinale rhizomes were obtained from local markets in the Basrah Governorate and kept in polyethylene bags at room temperature until use. The plant samples were ground with an electric grinder by Isolab to obtain a fine powder. The plants were stored in dark, tightly sealed glass containers at a temperature of 4°C until use.

Z. officinale plants were classified at the University of Basra - College of Science, Dep. of Biology, as follows: Kingdom: Plantae, Phylum (Division): Tracheophyta, Class: Liliopsida, Order: Zingiberales, Family: Zingiberaceae, Genes: Zingiber, Species: *Zingiber officinale*.

2.2. Isolation and identification of essential oils

The essential oils were extracted using a Clevenger apparatus by removing 25 gm of the ground material, adding 500 ml of glass, adding 250 ml of distilled water, and heating at 60–80°C for 4 hours. The essential oil compounds were separated using gas chromatography–mass spectrometry analysis (Zhang et al., 2020).

2.3. Diagnosis of essential oils using GC–MS technology

Gas chromatography–mass spectrometryspectrometry (GC–MS) was used to analyze the compounds of *Z. officinale* in GC–MS laboratories at the College of Agriculture, University of Basrah (SHMADZU, Japan; GC MS QP 2010 Ultra, equipped with a capillary column type (DB-MS). 5% phenyl, 95% methylpoly siloxane as a static phase; its dimensions are 30 m in length and 0.32 m in diameter, and the thickness of the static phase is 0.25 micrometres. High-purity helium gas (99.9) was used. The injection process was carried out with an automatic injector (SHMADZU, 20i+S Aoc).

2.4. Preparation of the drugs

Atenolol tablets (from TAJ Pharma) with a concentration of 50 mg were manually ground and subsequently dissolved in 50 ml of distilled water. The animals were dosed after the appropriate concentration was calculated according to their body weight.

2.5. Histological Study

The present study was completed on healthy adult male Wistar albino rats (*Rattus norvegicus*) aged 10-12 weeks with an average weight ranging between 200 and 250 gm. The animals were maintained in plastic cages under controlled standard conditions in an air conditioner at a temperature of 25 ± 2°C throughout the experimentation phase (Gravian et al., 2007). There were a total of 60 adult male rats (*Rattus norvegicus*), and there were six groups of rats, with ten rats in each group: the first group was the control group, the second group was treated with the atenolol drug, and the third group was treated with the atenolol drug + ginger oil (Ara et al., 2008, Akinyemi & Adeniyi, 2018).

3. Results and Discussion

The essential oils extracted from the *Z. officinale* rhizomes were light yellow in color and had a pungent and spicy taste. The amount of oil extracted was 1% according to the following equation (Abbas et al., 2021):

$$Extraction\ percentage = Extract\ weight/plant\ weight \times 100$$

The chemical compound extraction results are shown in Table 1 and Figure 1. There were 38 essential oils extracted from the *Z. officinale* rhizomes. Sesquiterpenes constituted 60% of the total percentage of compounds produced if 17 compounds were present, followed by monoterpenes, which constituted 30% if 10 compounds were present. In addition, the results showed that beta-sesquiphellandrene had the highest percentage among the essential compounds (28.94%), followed by 2-butanone, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, and (R)- (16.82%), followed by alpha.-farnesene (14.45%). The remaining compounds constituted a smaller percentage of the population; they were represented by Zingiberene, beta.-phellandrene, camphene, 1,8-cineole, alpha-cedrene, elemol, and Shogaol.

The total terpenoid compounds were 25.6% monoterpenes and 43.58% sesquiterpenes; these percentages are considered similar to those of Syafri et al. (2022). and agreed with him by finding camphene and 1,8-cineole in *Z. officinale*. Our results agreed with those of most other researchers, who reported that *Z. officinale* contains zingiberene, camphene, α-farnesene, sesquiphellandrene, elemol, [6]-shogaol, and α-curcumene. In addition, zingiberene and 1.8-cinéol were found (Tarfaouil et al. 2022). Gingerols and shogaols are the main volatile substances found in the rhizomes of *Z. officinale,* and they have gained recognition for their role in promoting human nutrition and health (Semwal et al., 2015). Shogaols and gingerols both have various biological functions, such as oxidant, antimicrobial, anti-inflammatory, anticancer, antioxidant, and antiallergic effects on various activities of the central nervous system. In addition to our findings being similar to those of Parvez et al. (2022), several chemical compounds, such as linalool, camphene, 1.8-cineol, camphor, β-elemene, ar-curcumene, α-zingiberene, and α-terpineol, were identified in the present study. The varied biological activities of Shogaols make them valuable biomarkers for quality control in a variety of ginger-containing products. Johnson et al. (2021) reported that the method of extracting ginger results in the production of different compounds. Liquid chromatography with high performance (HPLC) was utilized to identify the 6-shogaols and gingerols, and gas chromatography (GC–MS) was used to identify additional gingerol derivatives. The wide range of compositions of essential oils is due to a combination of factors, such as farming practices, analytical techniques, cultivated varieties, and climates (Nampoothiri et al., 2012; Mangprayool et al., 2013; Mesomo et al., 2013). Furthermore, it has been demonstrated that storage duration and drying procedures have a major impact on citral content (Sekiwa-Iijima et al., 2001; El-Ghorab et al., 2010).
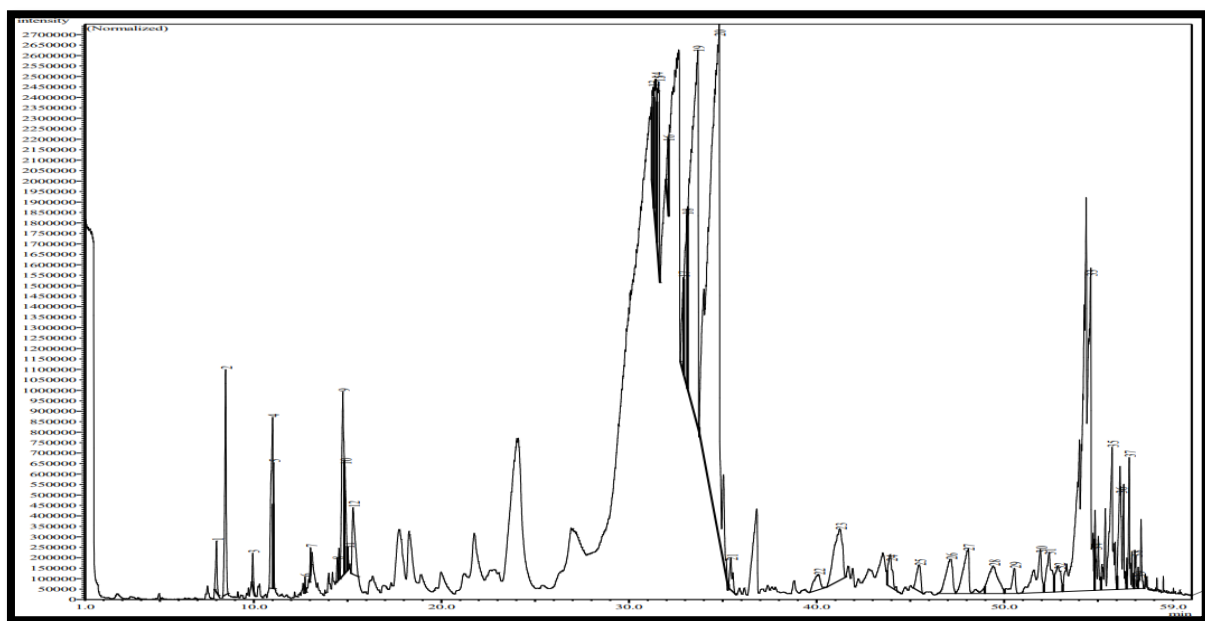

Figure 1 Histogram spectrum of essential oils in Z. officinale rhizomes determined using GC–MS.

3.1 Histological sections of the adrenal gland

The adrenal glands of the control animals exhibited two layers in histological sections: an outer layer known as the cortex, surrounded by a fibrous capsule, and three regions, the first of which is the glomerular region, which consists of rounded clusters of columnar or pyramidal cells. The thick middle layer, the zona fasciculata, consists of long cords of large, spongy-looking cells and the reticularis zone, and the inner layer, the medulla, is small, has fewer lipid droplets and consists of chromaffin cells that are arranged in ovoid clusters near capillaries (Figure 2 A, B). Treatment of the rats with the atenolol drug revealed that the cortex was composed of atrophied zona granulosa, vascularized and inflamed zona fasciculate tissue and severe inflammation of the zona reticularis, while the medulla exhibited mild hemorrhaging that extended between the chromaffin cells. The parenchyma of the medulla consisted of loosely disorganized clusters and cords resembling the epithelium (epitheliod cells). The zona glomerulosa cells were small and columnar beneath the fibrous capsule, and the cells

showed degenerated nuclei. The zona fasciculate cell population was intermediate, and the largest layer of cortex was large. Additionally, the cells were polyhedral in shape and appeared empty in sections separated by sinusoidal capillaries, while the deep layer was zona reticularis formed by pink-stained cells and an irregular arrangement (Figure 2 C, D). There was the same normal histological presentation with few to mild distortion. The zona glomerulosa was normal with pyknotic nuclei, a normal capsule thickness, mild hemorrhage within the capsular septa, and a zona fasciculate consisting of pyramid cells; nevertheless, there were crowded nuclei with mild hemorrhage. The zona reticularis looked dense with smaller cells, normal nuclei and eosinophilic cytoplasm, and this layer was in contact with the upper layer of the zona fasciculate (Figure 3 A, B). While the interaction between atenolol and ginger had mild moderate changes in different adrenal zones, the zona glomerulosa had a normal structure and a small cluster beneath the capsule with crowded nuclei; the zona fasiculata had broad bands of large cells and a mild hemorrhage area; the cells appeared to resemble lipoblasts; the innermost zona was the zona reticularis and consisted of smaller cells with irregularly arranged, richly vascularized, capsular blood vessels penetrating this layer through connective tissue septa; and the ginger plant ameliorated the severe changes caused by atenolol (Figure 3 C, D).

Table 1 Essential oil compounds in the *Z. officinale* rhizome according to GC–MS technology.

Peak	Retention time	Area%	Chemical formula	Name
1	8.012	0.37	$C_{10}H_{16}$	2-Norpinene
2	8.502	1.75	$C_{10}H_{16}$	Camphene
3	9.950	0.18	$C_8H_{14}O$	5-Hepten-2-one, 6-methyl-
4	11.004	1.87	$C_{10}H_{16}$	beta.-Phellandrene
5	11.062	0.43	$C_{10}H_{18}O$	Eucalyptol (1,8-Cineole)
6	12.735	0.06	$C_9H_{18}O$	2-Nonanone
7	13.027	0.09	$C_{10}H_{20}O$	Linolool
8	14.445	0.18	$C_{10}H_{18}O$	Isoborneol
9	14.750	2.21	$C_{13}H_{22}O$	Bicyclo[2.2.1]heptan-2-ol, 1,7,7trimethyl-, (1S-endo)-
10	14.860	0.93	$C_{10}H_{18}O$	L-4-terpineol
11	15.020	0.12	$C_{10}H_{18}O$	Santolina alcohol
12	15.297	1.07	$C_{10}H_{18}O$	Alpha.-Terpieol
13	31.277	3.27	$C_{15}H_{22}$	Curcumene
14	31.455	1.78	$C_{15}H_{24}$	Alpha-Cedrene
15	31.577	2.19	$C_{15}H_{22}$	Benzene,1-(1,5-dimethyl-4-hexenyl)-4-methyl-
16	32.070	0.60	$C_{15}H_{24}$	Di-epi-.alpha.-cedrene
17	33.080	3.37	$C_{15}H_{24}$	Zingiberene
18	33.665	14.45	$C_{15}H_{24}$	alpha.-Farnesene
19	34.797	28.94	$C_{15}H_{24}$	beta-Sesquiphellandrene
20	35.452	0.45	$C_{15}H_{26}O$	Elemol
21	40.104	0.56	$C_{17}H_{28}O_2$	Gamma-Eudesmol
22	41.262	2.43	$C_{15}H_{26}O$	Guaiyl acetate or Bulnesol
23	43.970	0.71	$C_{15}H_{26}O$	.alpha.-Cadinol
24	45.483	0.60	$C_{15}H_{24}$	3-Cyclohexen-1-ol,1-(1,5-dimethyl-4-hexenyl)-4-methyl-
25	47.157	1.28	$C_{12}H_{22}O$	Cyclopropanemethanol, .alpha.,2-dimethyl-2-(4-methyl-3-pentenyl)-, [1.alpha.(R*),2.alp
26	48.070	1.59	$C_{15}H_{24}O$	6,10-Dodecadien-1-yn-3-ol,3,7,11 trimethyl-
27	49.431	1.46	$C_{13}H_{22}O$	2-Butanone,4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (R)-
28	50.562	0.55	$C_{11}H_{18}O_2$	2(1H)-Naphthalenone, octahydro-8a-hydroxy-4a-methyl-
29	51.948	1.56	$C_{15}H_{26}O$	Epiglobulol
30	52.413	1.11	$C_{15}H_{24}O$	Aromadendrene oxide-(2)
31	52.920	0.76	$C_{15}H_{24}O$	Isoaromadendrene epoxide
32	54.605	16.82	$C_{13}H_{22}O$	2-Butanone,4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-,(R)-
33	54.870	0.89	$C_{10}H_{24}O_3Si$	Silane, dimethyl(4-methoxy-2-methylbutoxy)ethoxy-
34	55.756	3.28	$C_{13}H_{22}O$	Bicyclo[2.2.1]heptan-2-ol,2-allyl-1,7,7-trimethyl-
35	56.203	2.39	$C_{15}H_{28}O$	2,10-Dodecadien-1-ol,3,7,11-trimethyl-, (E)-(.+/-.)-
36	56.670	1.12	$C_{15}H_{22}$	Benzene,1-(1,5-dimethyl-4-hexenyl)-4-methyl-
37	57.008	0.28	$C_{22}H_{42}S_2Si$	Shogaol
38	57.173	0.51	$C_{16}H_{26}O_3$	2-Dodecen-1-yl(-)succinic anhydride
		100.00		

The adrenal gland has been reported to be highly sensitive to toxicity and to the most common location of endocrine lesions, making it extremely vulnerable to chemical assault (Ribelin, 1984; Harvey, 1999). Marcello (2001) revealed that high doses of ginger aqueous extract distorted the histology of adrenal gland tissues, while low concentrations did not affect adrenal gland tissues. The findings of the present study may be in line with those of previous studies showing that high or

reasonable consumption of ginger has negative side effects. Amin and Hamza (2006) demonstrated that *Z. officinal* increased the activities of testicular antioxidant enzymes, superoxide dismutase, glutathione and catalase and reduced the level of malondialdehyde. *Z. officinale* has mediating effects on adrenal glands caused by treatment with mancozeb via its potent antioxidant action (Sakr et al., 2010). Histopathological examination of the protective effect of Z. officinale in rats was also confirmed (Sakr et al., 2010). These differences may be due to the antioxidative properties of ginger, as described by Fakunle et al. (2013). After CCl4-induced toxicity in Wistar rats, *Z. officinale* provides a few protective measures that improve pyramidal and polyhedral cells in the adrenal cortex and further validate its antioxidative) potential (Fakunle et al., 2013; Ezejindu et al., 2014). The mean body weight of the rats decreased after treatment with *Z. officinale,* and histopathological analysis revealed abnormalities in the zona glomerulosa, suggesting that high consumption of ginger may distort the adrenal gland. Conversely, *Z. officinale* may reduce the inflammatory response, ameliorate shock reversal, and normalize microcirculatory abnormalities and the adrenal gland glucocorticoid concentration (Lai et al. 2018). Previous research has shown that *Z. officinale* protects experimental animals against anticancer medication-related damage (Ajith et al., 2008).
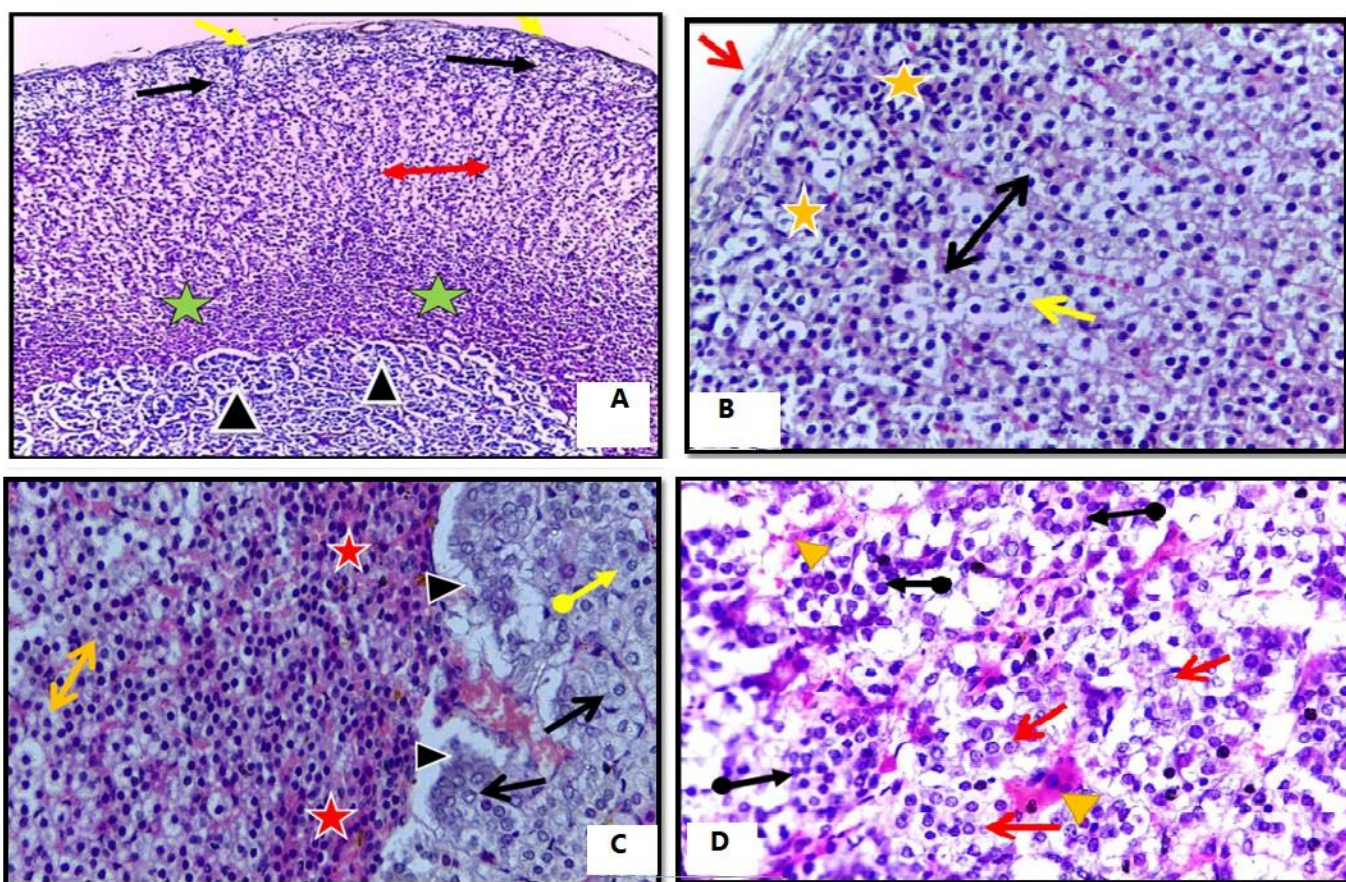

Figure (2) A: Section in normal adrenal gland showed fibrous capsule (→), normal zona glomerulosa (→) as cluster of small cells, broad layer of zona. fasiculata (↔) consist cells arranged in parallel cords and zona reticularis (★) surrounding the medulla that contain chromaffin cells that are arranged in ovoid clusters (▲).
B: Section in normal adrenal gland showed capsule (→) surrounded the gland, glomerulus region (★), as small cluster, zona fasciculate (↔) with large pyramide cells, pyknotic nuclei (→). C: Section in adrenal gland from rats treated with atenolol showed medulla (→), chromaffin cells (→), pink staining zona reticularis (★), vacuolation of spongiocytes (↔) and no connective tissue (▶) separated cortex from medulla. D: Section in adrenal gland from rats treated with atenolol showed the changes in medulla, referred to chromaffin cells (→) with pale nuclei, cluster of ganglion cells (→) and mild hemorrhage (▶). (H&E) stain (40X). stain (40 X).

4. Conclusions

From the current investigation, it can be concluded that the main component of *Z. officinale* essential oil rhizomes is beta-sesquiphellandrene, which had the highest percentage among the essential compounds, followed by alpha-farnesene and a smaller percentage from Zingiberene, beta-phellandrene, camphene, 1,8-cineole, alpha-cedrene, elemol, and Shogaol.

These compounds have a variety of biological functions, such as anti-inflammatory, anticancer, antioxidant, and antiallergic effects (Parvez et al., 2022). *Z. officinale* essential oil significantly reduced histological and cellular changes in the adrenal gland after treatment with atenolol. The results of this study indicate that the mechanism of action of these *Z. officinale* strains is protective on the adrenal gland. Therefore, *Z. officinale* might be a potential therapy for improving adrenal responsiveness and patient outcomes.
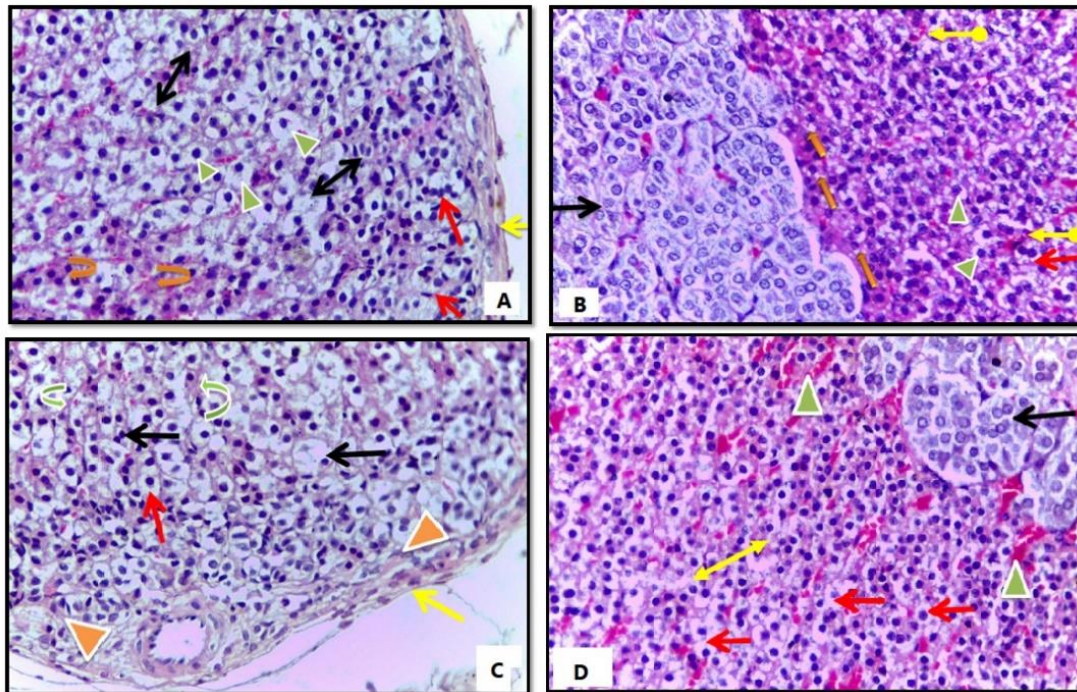

Figure (3) A: Section in adrenal gland from rats treated with ginger showed normal capsule ( ) consist of connective tissue, normal Z. glomerulosa ( ) as cluster of small cells, broad layer of Z. fasiculata ( ) consist of large cells looked similar to lipoblast ( ) and mild hemorrhage ( ) within capsule septa.

B : Section in adrenal gland from rats treated with ginger showed the Z.fasiculata ( ), and z. reticularis ( ) consist of small cells with pyknotic nuclei ( ), mild hemorrhage ( ) and mild lipid droplet ( ) also noticed.

C: Photomicrograph of darnel gland section in rats treated with atenolol and ginger oil showed normal capsule ( ) zona glomurulosa ( ) as small cluster, zona fasciculate ( ) with large pyramide cells, pyknotic nuclei ( ) and thin septa from capsule ( ).

D : Photomicrograph of darnel gland section in rats treated with atenolol and ginger oil showed part from zona fasciculate ( ) with crowded and irregular nuclei, rich vascularized zona reticularis ( ), mild hemorrhage ( ), mild vacuolation in small cells ( ) of zona reticularis. (H&E) stain (40X).

Ethical considerations

This study was conducted following the approval of the scientific and ethics committees of Basrah University and the Iraqi Ministry of Health (numbered 125 dated 10/07/2022). Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest

On behalf of all the authors, the corresponding author states that there are no conflicts of interest.

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