INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES & TECHNOLOGY

e-ISSN:2455-5134; p-ISSN: 2455-9059

PREPARATION OF SALVIA OFFICINALIS L. EXTRACT AND STUDY OF ITS EFFECT ON SOME PHYSIOLOGICAL VARIABLES IN ALBINO RATS

***Mohammed A. Ajeel, *Khadeeja Y. Abid, **Wijdan I.A. Abd-Alwahab**

*College of Pharmacy, University of Mosul, Mosul, Iraq
**College of Education, University of Samarra,
Samarra, Iraq

Paper Received: 18th June, 2021; **Paper Accepted:** 12th August, 2021;
Paper Published: 14th August, 2021

DOI: http://doi.org/10.37648/ijrmst.v11i02.002

How to cite the article:

Mohammed A. Ajeel, Khadeeja Y. Abid, Wijdan I.A. Abd-Alwahab, Preparation of Salvia Officinalis L. Extract and Study of its Effect on Some Physiological Variables in Albino Rats, IJRMST, July-December 2021, Vol 12, 16-33, DOI: http://doi.org/10.37648/ijrmst.v11i02.002

ABSTRACT

Salvia officinalis is one of the most valued herbs because of its high amount of essential oil and its many components. It has many health-related uses such as improving cognition, as well as reducing the amount of nursing mother's milk during weaning, also recommended for the gargling of the infectious throat, and to treat cardiovascular diseases and nervous disturbance, depression, cerebral ischemia and acts as an antiseptic for wounds. This study aim was to prepare the plant extract of *Salvia officinalis L.* from the Iraq local areas, determine its chemical properties and study its effect on some physiological and immunological variables in white rats. The plant leave Extract was Prepared and its effects were assessed on several physiological parameters using 20 male rats. The rats were divided into four groups. the control group(G1) received standard food and water; the negative control group (G2) received fat rich diet; G3 rats were given *Salvia officinalis* with a concentration of 100 mg\ kg\day. G4: rats were given *Salvia officinalis* 100mg/kg body weight and received fat rich diet. Roche/Hitachi, cobas c 501/502 were used to evaluate the levels of aminotransferase Enzymes, Aspartate transaminase (AST), Alanine aminotransferase (ALT), alkaline phosphatase enzyme (ALP), serum creatinine, serum urea, total protein, albumin, cholesterol, triglyceride, and high-density lipoprotein (HDL). While Globulin concentration, very Low-Density Lipoprotein (VLDL), and Low-Density Lipoprotein (LDL) were calculated according to some referred equations. The phytochemical analysis showed that the compounds identified in the sample were found to be alkaloids, phenols, tannins, coumarins glycosides, flavonoids, quinines, Carbohydrates and steroids. The results showed a significant increase ($P < 0.01$) in the level of liver enzymes ALT, AST and ALP, in the G2 treated with the high fat diet compared with a control group and showed a significant increase ($P < 0.01$) in the level of urea and creatinine in animal serum treated with high fat food compared to the control group. Animals administrated with *Salvia officinalis* (G3 and 4) were significantly increase ($P < 0.01$) the levels of the levels of Total Protein, Albumin, and Globulin in comparison with rats in the G2 group. Administration with *Salvia officinalis* in G4 group reduced ($P < 0.01$) the Triglycerides, (VLDL-C), and (LDL-C) and markedly enhanced HDL levels ($P < 0.01$) in G3 group compared with G4 group.

Keywords: *Salvia Officinalis, Extraction, Rat, Cholesterol, Triglycerides, HDL-c.*

INTRODUCTION

Salvia officinalis (Sage) is a multipurpose culinary herb belonging to the families of Lamiaceae/Labiatae. It is also known as Gardensage, Common Sauge or Culinary Sauge. It is a fragrant, permanent, woody subshrub that comes from the northern Mediterranean region and is extensively spread throughout the slopes and beaches

of Southern Europe. It is cultivated in Europe and the United States, Spain and Italy in particular [1] [2]. It has been utilized as a culinary herb in many nations and is currently grown worldwide for dried leaves which are used as a raw material for the pharmaceutical, perfume and food industries. [3].

It is one of the most valued herbs because of its high amount of essential oil and its many components [4]. It has many health-related uses such as improving cognition, as well as reducing the amount of nursing mother's milk during weaning, also recommended for the gargling of the infectious throat, and to treat cardiovascular diseases and nervous disturbance, depression, and cerebral ischemia. It acts as an antiseptic for wounds [5][6][7].

The species is a well-recognized plant in the food industry, pharmaceutical industry and cosmetics industry. It's a well-known herb. The areal portions (Salvia folium) are included as a natural source for food flavour, in various European Pharmacopeias [8]. And was serving as an antidiabetic [9][5], antioxidant [10], anti-inflammatory [11], antimicrobial [12], antiviral [13], gastroprotective and antimutagen [14] agent. It has also been shown to be beneficial in the treatment of cardiovascular and cancer disorders.[15][16] as well as in the treatment of depression and neurological disorders [17][18]

S. Officinalis has been employed in both traditional medicine and clinical studies to treat menopausal symptoms. Hot flashes, sleeplessness, night-time sweating, dizziness, migraines, and palpitations are some of the symptoms. [19][20]

S. Officinalis leaf preparations have long been used as a diabetic treatment. Swanston-Flatt et al. examined the possible anti-diabetic effects of S. Officinalis extract against type I and type II diabetes [9]. According to their findings, ethanol extracts of S. Officinalis considerably lower blood glucose in healthy rats and hyperglycemia in type I diabetic rats [21]. Furthermore, Eidi et al discovered that the methanolic extracts of S. Officinalis reduces blood glucose in type I diabetes while having no effect on insulin production by pancreas [22]. Lima et al. discovered that a tea preparation of S. Officinalis decreases glucose production by the liver while increased insulin action in type II diabetes, comparable to metformin, which is commonly used in the therapeutic treatment of diabetes [23]. Patenkovi et al. revealed the possible antimutagenic activity of S. Officinalis tea, which may

operate via suppressing metabolism via antioxidative action [24].

Fresh S. Officinalis extracts used once daily exhibited good therapeutic value in terms of safety, effectiveness, and tolerance in the treatment of menopausal symptoms. S. Officinalis is also renowned for its ability to help with memory problems, depression, and cerebral ischemia [25]. S. Officinalis as well as used to treat Alzheimer's disease, with essential oil acting as an acetylcholinesterase (that might play a major role in the memory loss) inhibitors, and increasing acetylcholine, a neurotransmitter component involved in signal transmission among synapses [23]. A number of studies have shown indicated that S. Officinalis enhances memory and cognition [17].

S. Officinalis is safe to use at prescribed doses, and there have been no complaints of harmful side effects [26]. However, recommended dosages should thus never be overrun and S. Officinalis formulations should never be taken for longer durations. The negative impact could appear due to the high thujone concentration [11]. Furthermore, the overuse of its products caused many disorders for the nervous as well as dementia and seizures [27]. The aim of current study to prepare the plant extract of *Salvia officinalis* L. from the Iraq local areas, determine its chemical properties and study its effect on some physiological and immunological variables in white rats.

MATERIALS AND METHODS

Preparation of Extract

The leaves of *Salvia officinalis* were obtained from Mosul market's /Iraq. The dried leaves *Salvia officinalis* was converted in to powder with the help of grinder for 30s. The dry leaves powder sample (15gm) was extracted using 80%methanol solvent (250 ml) for 24hrs using Soxhlet extractor until complete extraction. After extraction, the methanol extract was evaporated using a rotary evaporator under pressure for 30 min the resulting is solid crude extract. Then dry crude extract weighted (3.41 g) was transferred into test-tube for antioxidant activity, and phytochemical screening. [28]

Phytochemical Screening

Phytochemical screenings of *Salvia officinalis* extract were assessed by standard methods. These include detection the founding of alkaloids, terpenoids, phenols, tannins, carbohydrates, saponins, glycosides, flavonoids, quinines, and steroids. [29][30].

Assessment of *Salvia officinalis* effects

Male albino rats (20 rats) were used to assess the effects of *Salvia officinalis* in vivo on the physiological parameters. The lab animals were obtained from the Central Animal House Facility of Zakho University their ages ranged from 7 to 9 weeks and weight:(180 - 200 g). The rats were kept in the filter-protected and air-conditioned room with constant temperature (21–25 c°), the humidity of 50–60%, and photoperiod of 12 h. After one week of acclimatization, were randomly divided into six groups each group contains 3 animals.

The first group (**G1**: **the control group**) received standard food and water. The second group was (**G2**) **the negative control group** received the `animal's food and fat (30%) [31] for 2 months. **G3:(***Salvia officinalis* group) rats were given *Salvia officinalis* with a concentration of 100 mg\ kg\day [31] for 2 months. **G4:** (*Salvia officinalis* **+ fat rich diet**) rats were given *Salvia officinalis* 100mg/kg body weight and received fat (30%) rich diet for 2 months.

Animal Anesthesia and Dissection

At the end of the study, the study rats were anesthetized using chloroform and then Compassionately slaughtered. blood was collected and centrifuged to obtain the serum in order to evaluate the other parameters of the study.

THE STUDY PARAMETERS

Measurement of some study parameters.

Concentrations of Aminotransferase Enzymes AST, ALT, alkaline phosphatase enzyme ALP, serum creatinine, serum urea, total protein, albumin, cholesterol, triglyceride, and high-density lipoprotein (HDL) were measured using (Roche/Hitachi, cobas c 501/502).

Calculation of some study parameters:

Globulin concentration, VLDL-C, and LDL-C, concentration was calculated according to the following equations.

Globulin= Total Protein con. -Albumin con. [32],[33]

VLDL-C = $\frac{Triglycerides\ concentration}{5}$. [34]

LDL-C= cholesterol – (HDL + VLDL-C). [34],[35].

Statistical analysis:

SPSS statistical program was used to analyze the results of the experiments. The ANOVA Duncan test was used to compare

the studied groups and the control group. The $p < 0.01$ were used four mean comparisons.

RESULTS

Characterization of bioactive compounds

The extract was subjected to phytochemical analysis. This resulted in the determination of bioactive compounds that were present in the methanol sample of plant extract. The compounds identified in the sample were found to be alkaloids, phenols, tannins, coumarins glycosides, flavonoids, quinines, Carbohydrates and steroids. The results are shown in table1.

Table 1. Phytochemical analysis of *Salvia officinalis* extract.

Phytoconstituents	methanol extract
Alkaloids	+ve
Flavonoids	+ve
Terpenoids	-ve
Tannin	++ve
Steroids	+ve
Phenols	+ve
Coumarine glycoside	+ve
Quinine	+ve
Protein	-ve
Carbohydrates	+ve
Saponine	-ve

Liver Enzymes

The results of the statistical analysis showed a significant increase (P <0.01) in the level of liver enzymes ALP, ALT, AST in the G2 group treated with the high fat diet compared with a control group.

Urea and Creatinine level

The results showed a significant increase (P <0.01) in the level of urea and creatinine in animal serum treated with high fat food compared to the control group.

Table 2. Showing the effect of the *Salvia officinalis* extract on some liver enzymes and urea and creatinine in white male rats of the study

Groups	Cr (mg/dl)	Urea (mg/dl)	ALP (U/L)	ALT (U/L)	AST (U/L)
G1	0.543 ±0.0277d	18.532 ±0.255d	82.85 ±0.203b	11.661 ±0.126d	16.877 ±0.175c
G2	0.962 ±0.01a	45.194 ±0.22a	91.11 ±0.014a	26.43 ±0.024a	28.563 ±0.027a
G3	0.602 ±0.06c	34.919 ±0.247b	73.55 ±0.017c	16.543 ±0.06c	17.518 ±0.131c
G4	0.723 ±0.05b	23.921 ±0.154c	83.822 ±0.015b	19.864 ±0.09b	21.869 ±0.07b

Note: Different letter (a,b,c..) within each column indicate significant differences ($p \leq 0.01$), Data are presented as the means ± standard deviation, (G1) normal control group, (G2) fat diet group, (G3) *Salvia officinalis* group, (G4) *Salvia officinalis* + fat diet group , There were 5 rats in each group of experiment.

Effect of *Salvia officinal is* on Total Protein, Albumin, and Globulin levels.

Table 3, shows that administration of fat diet in G2 significantly reduced the levels of Total Protein, Albumin, and Globulin in comparison with the normal rats G1 group ($p < 0.01$), while animals administrated with *Salvia officinalis* (G3 and 4) were significantly increase the levels of the mentioned parameters in comparison with rats in the G2 group.

Table 3. Effects effect of the *Salvia officinalis* extract on Serum Total Protein, Albumin, and Globulin levels.

Groups	Total Protein *(g/dl)*	Album *(g/dl)*	Globul *(g/dl)*
G1	7.120 ±0.34a	5.370 ±0.01a	1.750 ±0.16b
G2	4.450 ±0.39c	3.320 ±0.01d	1.130 ±0.01c
G3	6.980 ±0.19a	4.820 ±0.01b	2.160 ±0.01a
G4	5.983 ±0.01b	4.110 ±0.01c	1.873 ±0.015b

Note: Different letter (a,b,c..) within each column indicate significant differences ($p \leq 0.01$), Data are presented as means ± standard deviation.

(G1) normal control group, (G2) fat diet group, (G3) *Salvia officinalis* group, (G4)

Salvia officinalis + fat diet group , There were 5 rats in each group of experiment.

Effect of *Salvia officinal is* on lipid profile and Phospholipids levels.

Table 4 shown that the effects of *Salvia officinalis* on lipid profile and Phospholipids in serum ($p < 0.01$) the results indicated that administration of fat diet in G2 group has a negative effect on High density lipoprotein cholesterol (HDL), while it elevated the Cholesterol, Triglycerides, very low-density lipoprotein cholesterol concentration (VLDL-C), low density lipoprotein cholesterol concentration (LDL-C) and Phospholipids levels. However, administration with *Salvia officinalis* in G4 group reduced those Triglycerides, (VLDL-C), and (LDL-C) levels. Furthermore, the intervention of *Salvia officinalis* markedly enhanced HDL levels in G3 group compared with G4 group.

Table 4: Effect of the *Salvia officinalis* extract on Cholesterol, Triglycerides, HDL, VLDL-C, and LDL-C.

Groups	TC *(mg/dl)*	TG *(mg/dl)*	HDL *(mg/dl)*	VLDL-C *(mg/100ml)*	LDL-C *(mg/100ml)*
G1	46 ±1.65c	48 ±1.05c	28 ±2.12c	9.6 ±0.210c	8.4 ±0.200c
G2	73 ±1.80a	76 ±1.30a	26 ±1.83d	15.2 ±0.26a	31.8 ±0.200a
G3	53 ±1.02b	41 ±1.03d	39 ±1.92a	9.2 ±0.206c	5.8 ±0.200d
G4	56 ±1.65b	67 ±1.05b	33 ±1.55b	13.4 ±0.210b	9.6 ±0.200b

. Note: Different letter (a,b,c..) within each column indicate significant differences ($p \leq 0.01$), Data are presented as the means ± standard deviation, (G1) normal control group, (G2) fat diet group, (G3) *Salvia officinalis* group, (G4) *Salvia officinalis* + fat diet group , There were 5 rats in each group of experiment.

DISCUSSION

The current investigation results have shown that the liver enzymes (ALT and AST) and alkaline phosphatase levels have significantly increased. these findings agreed with research [31], which proved this by examining the tissue samples of the liver and found necrosis that might result in the bloodstream release of these enzymes [36]. High-fat diets have a favorable connection with liver illness via steatosis and a rise in saturated fatty acids in the liver, which coincide with acute hepatic tissue damage, boosting the release of liver enzymes into the circulation, as shown by Zhang and his colleagues [37]. This might be explained by the presence of oxidative damage and free radical production in hyperlipidemic mice [38]. A high-fat diet promotes peroxidation in the liver, heart, and kidneys, and the liver is rich in mitochondrial tissue. As a result, it is much more vulnerable to free radical's damage, which affects the function of the mitochondria and impairs the electron transport chain efficiency, and leads to the apoptosis process [39].

The alterations produced by elevated MDA in the liver cells, which harm mitochondrial activities, cause oxidation process of nucleotide, lipid, and endoplasmic reticulum enzymes, specifically glucose-6-phosphatase and cytochrome p-450. As a consequence, numerous enzymes are released out of the lysosomes, increasing the plasma membrane permeability and, causing damage[40] to hepatic cells and, as a result, the releasing of their enzymes. The current findings, on the other hand, revealed a significant ($P < 0.05$) reduction in the level of the liver enzymes in the groups that were treated with *Salvia officinalis* leaf extract compared to the T1 group fed a fat-rich diet [41]. These findings support a previous study that found *Salvia officinalis* leaf extract to be effective versus hepatocyte damage in mice fed a high-fat diet [42].

The decreased level of liver enzymes in rats treated with leaf extract is attributable to the plant's antioxidant components and their involvement in safeguarding organs and tissues from damage associated with oxidative stress produced by a high-fat diet [40].

Antioxidants, such as phenolic and flavonoid compounds, protect lipids in cellular membrane from severe oxidation and breakdown, preventing enzymes from being discharged into the serum [43]. That might be attributable to catechol, which

is a contributor to the synthesis process of rosmarinic acid and caffeic acid, which is recognized to demolish free radical damage in the body cells by shattering free radical chains through blocking the initiation and thus preventing the growth and reproductive capacity of the free radical's chain, and led to preventing the damage to hepatocytes and sustains the enzymes release into the bloodstream [44].

S. officinalis also provides zinc and selenium and prevents oxidative damage to the liver and kidneys produced by excess free radicals by boosting the potential of antioxidants like SOD, GSH, and GR [45]. It was also discovered that vitamin E and selenium were added to the dietary of the lab animals contributed to reducing cirrhosis through both the blocking and reduction of the hepatic satellite cells (HSC) which has an important role in the cirrhosis formation [46]. The zinc in the S.offisinalis is also playing an essential role in the metallothionine (MT) production, (a protein-rich in the cysteine amino acid), through a linkage between the thiol group of the cysteine terminals and the heavy metals in and therefore increase the antioxidant characteristics [47].

These results are agreed with Ahangarpour et al., that the rise in concentrations of creatinine and urea is due to higher total lipid oxidation [48] and, subsequently, lower concentrations of CAT and SOD enzymes, increasing the generation of oxidative agents resulting in oxidative stress [38].

Yao and his group Yao et al., noted in their in their investigation of the obesity effects on kidney function in rats model on the administration of high-fat meals Yao and his colleagues have hypothesized that kidney disorders induce renal macrophages inflammation and hypertrophy[49].

In another study, there was a considerable rise in blood cholesterol, triglycerides, LDL, and VLDL levels in high-fat diets compared to the control group and the findings of the study showed that the level of HDL-C decreased substantially when compared to the control group [50].

Furukawa et al. found an increase in morbidity in high-fat diets in rats and they proposed that this increases in morbidity can be ascribed to the fact that high-fat diets in rats produce oxidative stress, which can result in significant quantities of reactive oxygen (ROS) species [51]. Munshi et al notes that high-fat diets induced high levels of cholesterol, LDL, triglycerides and VLDL with lower HDL

because of an enhanced lipid peroxidation owing to retarded gastric drainage. This was verified in the same study that the build-up of the tiny lipids in the gut, which disrupts the mechanisms of antioxidant defence causing oxidative stress[52]. This might be due to the increase in the quantity of cholesterol in the diet, which would lead to a rise in the efficiency of the cholesterol absorption by the small intestine [53] resulting in an increase of fat accumulation in the liver, which enhances hepatocyte processing [54]. A fat diet can also induce a reductase (HMG-CoA reductase) called 3-methylglutaryl coenzyme A reductase, largely responsible for cholesterol production [55]. The decreased in HDL is likely related to a high fat diet, which decreases the activity of L-CAT (lecithin-cholesterol acyl transferase), a binding enzyme that plays an essential part in the production of HDL, and cholesterol flow from cell membranes toward the HDL [56].

The cause of the *Salvia officinalis* beneficial effect on lipid profile can be attributed to the contains potent compounds that block triglycerides production, such as single turbines, which are known to be thujone compound, recognized for reducing cholesterol and triglycerides. The drop in lipid concentrations can also be caused by the plant possessing flavonoids which reduce blood lipids as an antioxidant. Flavonoids also serve a direct function in enhancing LDL receptors in the liver and their interaction with protein B. Consequently, removes it from the blood. [43]. Interestingly, the hypolipedemic actions of *S officinalis* were comparable to hypolipidemic medications in current use [57],[58],[57],[59]; with more tolerable adverse effects profile compared to many chronic drugs in current use

CONCLUSIONS:

A conclusion can be drawn that *Salvia officinalis* alcohol extracted has a beneficial effect on the lipid profile especially and all the other parameters of the study parameters for all of the extract-treated groups (G3 and G4) compared to the negative control fat diet group (G2)

REFERENCES

[1] S. Glisic, J. Ivanovic, M. Ristic, and D. Skala, "Extraction of sage (Salvia officinalis L.) by supercritical CO2: Kinetic data, chemical composition and selectivity of diterpenes," *J. Supercrit. Fluids*, vol. 52, no. 1, pp. 62–70, 2010.

[2] V. Prakash, *Leafy spices*. CRC press, 2019.

[3] P. C. Santos-Gomes, R. M. Seabra, P. B. Andrade, and M. Fernandes-Ferreira, "Phenolic antioxidant compounds produced by in vitro shoots of sage (Salvia officinalis L.)," *Plant Sci.*, vol. 162, no. 6, pp. 981–987, 2002.

[4] C. A. Newall, L. A. Anderson, and J. D. Phillipson, *Herbal medicines. A guide for health-care professionals*. The pharmaceutical press, 1996.

[5] M. Hamidpour, R. Hamidpour, S. Hamidpour, and M. Shahlari, "Chemistry, pharmacology, and medicinal property of sage (Salvia) to prevent and cure illnesses such as obesity, diabetes, depression, dementia, lupus, autism, heart disease, and cancer," *J. Tradit. Complement. Med.*, vol. 4, no. 2, pp. 82–88, 2014.

[6] A. L. Lopresti, "Salvia (sage): a review of its potential cognitive-enhancing and protective effects," *Drugs R. D.*, vol. 17, no. 1, pp. 53–64, 2017.

[7] J. Mann, *Murder, magic, and medicine*. Oxford University Press, USA, 2000.

[8] T. Monograph, "European Pharmacopoeia," *Eur. Dir. Qual. Med. Heal. Care Counc. Eur. (EDQM), edn*, vol. 9, pp. 3104–3105, 2017.

[9] S. K. Swanston-Flatt, P. R. Flatt, C. Day, and C. J. Bailey, "Traditional dietary adjuncts for the treatment of diabetes mellitus," *Proc. Nutr. Soc.*, vol. 50, no. 3, pp. 641–651, 1991.

[10] S. Yadav and U. Mukundan, "In vitro antioxidant properties of Salvia coccinea Buc'hoz ex etl. and Salvia officinalis L," *Indian J Fundam Appl Life Sci*, vol. 1, pp. 232–238, 2011.

[11] D. Baricevic *et al.*, "Topical anti-inflammatory activity of Salvia officinalis L. leaves: the relevance of ursolic acid," *J. Ethnopharmacol.*, vol. 75, no. 2–3, pp. 125–132, 2001.

[12] R. Khalil and Z.-G. Li, "Antimicrobial activity of essential oil of Salvia officinalis L. collected in Syria," *African J. Biotechnol.*, vol. 10, no. 42, pp. 8397–8402, 2011.

[13] P. Schnitzler, S. Nolkemper, F. C. Stintzing, and J. Reichling, "Comparative in vitro study on the anti-herpetic effect of phytochemically characterized aqueous and ethanolic extracts of Salvia officinalis grown at two different locations," *Phytomedicine*, vol. 15, no. 1–2, pp. 62–70, 2008.

[14] W. K. D. Kahil, "Effects of Salvia officinalis extract and its nano-encapsulated form on methylmercury induced neurotoxic-stress in male rats," *World Appl. Sci. J*, vol. 24, pp. 826–837, 2013.

[15] D. F. N. Pedro, A. A. Ramos, C. F. Lima, F. Baltazar, and C. Pereira-Wilson, "Modulation of DNA damage prevention and signaling pathways in diet induced colon cancer prevention," in *BMC Proceedings*, 2010, vol. 4, no. 2, p. 1.

[16] M. Keshavarz, A. Bidmeshkipour, A. L. I. MOSTAFAEI, K. Mansouri, and M. H. R. MOHAMMADI, "Anti tumor activity of Salvia officinalis is due to its anti-angiogenic, anti-migratory and anti-proliferative effects," 2011.

[17] M. Eidi, A. Eidi, and M. Bahar, "Effects of Salvia officinalis L.(sage) leaves on memory retention and its interaction with the cholinergic system in rats," *Nutrition*, vol. 22, no. 3, pp. 321–326, 2006.

[18] A. Khan, N. ur Rehman, K. M. AlKharfy, and A.-H. Gilani, "Antidiarrheal and antispasmodic activities of Salvia officinalis are mediated through activation of K+ channels," ||| *Bangladesh J. Pharmacol.*, vol. 6, no. 2, pp. 111–116, 2011.

[19] K. Hostanska, J. Reichling, S. Bommer, M. Weber, and R. Saller, "Hyperforin a constituent of St John's wort (Hypericum perforatum L.) extract induces apoptosis by triggering activation of caspases and with hypericin synergistically exerts cytotoxicity towards human malignant cell lines," *Eur. J. Pharm. Biopharm.*, 2003, doi: 10.1016/S0939-6411(03)00046-8.

[20] S. G. Walch, L. Ngaba Tinzoh, B. F. Zimmermann, W. Stühlinger, and D. W. Lachenmeier, "Antioxidant capacity and polyphenolic composition as quality indicators for aqueous infusions of Salvia officinalis L.(sage tea)," *Front. Pharmacol.*, vol. 2, p. 79, 2011.

[21] F. J. Alarcon-Aguilar, R. Roman-Ramos, J. L. Flores-Saenz, and F. Aguirre-Garcia, "Investigation on the hypoglycaemic effects of extracts of four Mexican medicinal plants in normal and Alloxan-diabetic mice," *Phyther. Res.*, vol. 16, no. 4, pp. 383–386, 2002.

[22] M. Eidi, A. Eidi, and H. Zamanizadeh, "Effect of Salvia officinalis L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats," *J. Ethnopharmacol.*, vol. 100, no. 3, pp. 310–313, 2005.

[23] C. F. Lima, M. F. Azevedo, R. Araujo, M. Fernandes-Ferreira, and C. Pereira-Wilson, "Metformin-like effect of Salvia officinalis (common sage): is it useful in diabetes prevention?," *Br. J. Nutr.*, vol. 96, no. 2, pp. 326–333, 2006.

[24] A. Patenkovic, M. Stamenkovic-Radak, T. Banjanac, and M. Andjelkovic, "Antimutagenic effect of sage tea in the wing spot test of Drosophila melanogaster," *Food Chem. Toxicol.*, vol. 47, no. 1, pp. 180–183, 2009.

[25] N. S. L. Perry, C. Bollen, E. K. Perry, and C. Ballard, "Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial," *Pharmacol. Biochem. Behav.*, vol. 75, no. 3, pp. 651–659, 2003.

[26] N. T. J. Tildesley, D. O. Kennedy, E. K. Perry, C. G. Ballard, K. A. Wesnes, and A. B. Scholey, "Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers," *Physiol. Behav.*, vol. 83, no. 5, pp. 699–709, 2005.

[27] R. Tisserand and T. Balacs, "Essential oil safety," *Int J Aromather*, vol. 7, no. 3, pp. 28–32, 1996.

[28] S. Yadav and P. Kumar, "Production, isolation and identification of flavonoids from aerial parts of Hiptage benghalensis," *Int J Life Sci Pharma Res*, vol. 2, no. 3, pp. 1–5, 2012.

[29] A. J. Harborne, *Phytochemical methods a guide to modern techniques of plant analysis*. springer science & business media, 1998.

[30] S. Velavan, "Phytochemical techniques-a review," *World J. Sci. Res.*, vol. 1, no. 2, pp. 80–91, 2015.

[31] L. A. A. Allaithi and W. M. K. Al-Azawi, "Study of the effect of salvia officinalis leaves extract and xenical drug on some of the biochemical and histological parameters in the rats induced with hyperlipidemia," *Plant Arch.*, vol. 19, no. 2, pp. 1111–1122, 2019.

[32] V. A. Buzanovskii, "Determination of proteins in blood. Part 1: Determination of total protein and albumin," *Rev. J. Chem.*, vol. 7, no. 1, pp. 79–124, 2017, doi: 10.1134/s2079978017010010.

[33] H. Goldenberg and P. A. Drewes, "Direct photometric determination of globulin in serum.," *Clin. Chem.*, vol. 17, no. 5, pp. 358–362, 1971, doi: 10.1093/clinchem/17.5.358.

[34] P. W. Wilson, R. D. Abbott, R. J. Garrison, and W. P. Castelli, "Estimation of very-low-density lipoprotein cholesterol from data on triglyceride concentration in plasma," *Clin. Chem.*, vol. 27, no. 12, pp. 2008–2010, 1981, doi: 10.1093/clinchem/27.12.2008.

[35] T. Hirano, K. Nohtomi, S. Koba, A. Muroi, and Y. Ito, "A simple and precise method for measuring HDL-cholesterol subfractions by a single precipitation followed by homogenous HDL-cholesterol assay," *J. Lipid Res.*, vol. 49, no. 5, pp. 1130–1136, 2008, doi: 10.1194/jlr.D700027-JLR200.

[36] A. Uthandi and K. Ramasamy, "Hepatoprotective activity of sesame meal on high fat fed wistar rats," *Int. J. Sci. Res.*, vol. 2, no. 12, pp. 205–211, 2011.

[37] W. Zhang, L. Zhu, and J. Jiang, "Active ingredients from natural botanicals in the treatment of obesity," *Obes. Rev.*, vol. 15, no. 12, pp. 957–967, 2014.

[38] S. A. Noeman, H. E. Hamooda, and A. A. Baalash, "Biochemical study of oxidative stress markers in the liver, kidney and heart of high fat diet induced obesity in rats," *Diabetol. Metab. Syndr.*, vol. 3, no. 1, pp. 1–8, 2011.

[39] F. Amirkhizi, F. Siassi, S. Minaie, M. Djalali, A. Rahimi, and M. Chamari, "Is obesity associated with increased plasma lipid peroxidation and oxidative stress in women?," *Arya Atheroscler.*, vol. 2, no. 4, 2010.

[40] U. K. Kolac, M. C. Ustuner, N. Tekin, D. Ustuner, E. Colak, and E. Entok, "The anti-inflammatory and antioxidant effects of Salvia officinalis on lipopolysaccharide-

induced inflammation in rats," *J. Med. Food*, vol. 20, no. 12, pp. 1193–1200, 2017.

[41] G. Poli, E. Albano, and M. U. Dianzani, "The role of lipid peroxidation in liver damage," *Chem. Phys. Lipids*, vol. 45, no. 2–4, pp. 117–142, 1987.

[42] C. M. Sá, A. A. Ramos, M. F. Azevedo, C. F. Lima, M. Fernandes-Ferreira, and C. Pereira-Wilson, "Sage tea drinking improves lipid profile and antioxidant defences in humans," *Int. J. Mol. Sci.*, vol. 10, no. 9, pp. 3937–3950, 2009.

[43] S. Kianbakht, B. Abasi, M. Perham, and F. Hashem Dabaghian, "Antihyperlipidemic effects of Salvia officinalis L. leaf extract in patients with hyperlipidemia: A randomized double-blind placebo-controlled clinical trial," *Phyther. Res.*, vol. 25, no. 12, pp. 1849–1853, 2011, doi: 10.1002/ptr.3506.

[44] W. Bors, C. Michel, K. Stettmaier, Y. Lu, and L. Y. Foo, "Antioxidant mechanisms of polyphenolic caffeic acid oligomers, constituents of Salvia officinalis," *Biol. Res.*, vol. 37, no. 2, pp. 301–311, 2004, doi: 10.4067/S0716-97602004000200017.

[45] I. Rusyn, J. M. Peters, and M. L. Cunningham, "Modes of action and species-specific effects of di-(2-ethylhexyl) phthalate in the liver," *Crit. Rev. Toxicol.*, vol. 36, no. 5, pp. 459–479, 2006.

[46] X.-H. Shen *et al.*, "Effects of dietary supplementation with vitamin E and selenium on rat hepatic stellate cell apoptosis," *World J. Gastroenterol. Wjg*, vol. 11, no. 32, p. 4957, 2005.

[47] B. Ruttkay-Nedecky *et al.*, "The role of metallothionein in oxidative stress," *Int. J. Mol. Sci.*, vol. 14, no. 3, pp. 6044–6066, 2013.

[48] A. Ahangarpour, S. Alboghobeish, A. A. Oroojan, L. Zeidooni, A. Samimi, and G. Afshari, "Effects of combined exposure to chronic high-fat diet and arsenic on thyroid function and lipid profile in male mouse," *Biol. Trace Elem. Res.*, vol. 182, no. 1, pp. 37–48, 2018.

[49] X. Yao, X. Dong, H.-S. Zhang, Y. Wang, and X.-S. Liu, "Preventive effect of Aster tataricus on oxidative stress and biomarker of renal function in rat fed with high fat diet and sucrose diet.," *Biomed. Res.*, vol. 28, no. 4, 2017.

[50] X. Kong *et al.*, "Effect of lipid lowering tablet on blood lipid in hyperlipidemia model rats," *Saudi J. Biol. Sci.*, vol. 25, no. 4, pp. 715–718, 2018.

[51] S. Furukawa *et al.*, "Increased oxidative stress in obesity and its impact on metabolic syndrome," *J. Clin. Invest.*, vol. 114, no. 12, pp. 1752–1761, 2017.

[52] R. P. Munshi, S. G. Joshi, and B. N. Rane, "Development of an experimental diet model in rats to study hyperlipidemia and insulin resistance, markers for coronary heart disease," *Indian J. Pharmacol.*, vol. 46, no. 3, p. 270, 2014.

[53] D. Mathe, "Dyslipidemia and diabetes: animal models.," *Diabete Metab.*, vol. 21, no. 2, pp. 106–111, 1995.

[54] R. J. Havel and E. Rapaport, "Management of primary hyperlipidemia," *N. Engl. J. Med.*, vol. 332, no. 22, pp. 1491–1498, 1995.

[55] N. Wu *et al.*, "Activation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase during high fat diet feeding," *Biochim. Biophys. Acta (BBA)-Molecular Basis Dis.*, vol. 1832, no. 10, pp. 1560–1568, 2013.

[56] J. Hannon Hashim Al-Awadi, K. Hammed Rashid, and A. Jawad Hassen, "High fat diet induce hyperlipidemia incidences with sever changes in liver tissue of male albino rats: A histological and biochemical Study," *karbala J. Pharm. Sci.*, vol. 4, no. 6, pp. 21–32, 2013.

[57] H. M. Almukhtar, I. M. Faisal, and M. M. Merkhan, "Acute effect of atorvastatin in comparison with rosuvastatin on glucose homeostasis in hypercholesteremic patients," vol. 25, 2021.

[58] Z. Althanoon, I. M. Faisal, A. A. Ahmad, and M. M. Merkhan, "Pharmacological aspects of statins are relevant to their structural and physicochemical properties," *Syst. Rev. Pharm.*, vol. 11, no. 7, pp. 167–171, 2020, doi: 10.31838/srp.2020.7.27.

[59] H. M. Almukhtar, I. M. Faisal, and M. M. Merkhan, "Effects of statins on platelet count in hyperlipidemic patients," *Int. J. Pharm. Res.*, vol. 12, no. 2, pp. 2640–2644, 2020, doi: 10.31838/ijpr/2020.12.02.357.