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Protective role of Salvia officinalis against formalin induce nephrotoxicity in Swiss albino mice

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Abstract: *Formalin is a constituent from many item of daily use including foods, Thus this study aimed to evaluate the histological changes induced by formalin on the kidney of adult male mice and evaluating the possible ameliorative role of salvia officinalis. Healthy male albino mice 8-10 weeks old weighting 24 - 30 gm were divided equally into four groups (n = 15 per group). The first group was given only the standard diet and served as the control, the second group was treated orally with aqueous extract of S. officinalis leaves (120 mg/kg bw.) for 3 successive weeks , the third group was administered with formalin (2.4 ml/kg body weight) in drinking water for 3 successive weeks and the fourth group was Co-treated with formalin and S. officinalis. The specimens of kidney were processed for histological study by light microscopy. Histological examinations revealed that administration of formalin only exhibited marked glomerular and tubular lesion included vacuolization and swelling the lining epithelium of tubules, inflammatory cells infiltration and hemorrhage in the interstitial tissue, necrotic or desquamation lining epithelium in the luminal tubules, intratubular esinophilic casts in some renal tubules, completely obscured or stenosis urinary space of renal corpuscles, shrinkage glomeruli of some renal corpuscles with widening urinary space, many glomeruli appeared with less cellularily, dilation and congestion blood vessels. In contrast administration of S. officinalis along with formalin induced ameliorating change in renal tissue of formalin intoxicated mice.*
Key words: *Salvia officinalis, Formalin, Histpathological kidney, Mice*

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I. Introduction

Formalin is a harmful chemical content which has high toxicity and can cause cancer containing in wastewater. Formalin is used in non-food industry and corps preserving [1] . Formalin is a constituent from many item of daily use including foods. A 40% of formaldehyde in water is known as formalin [2]. Formaldehyde is a colorless flammable gas with a pungent odor, it is widely used in industrial and medical settings and is a major source of occupational pollution compound [3]. Formaldehyde metabolized by the liver is transferred into blood as format. The discharge of formaldehyde can be through urine as format salts or through lungs by turning into CO2 . Some of them enter into the carbon structure of protein and nucleic acids and are kept in the body [4] [5] 6] **[7]**. Formaldehyde is quickly absorbed from the gastrointestinal tract following ingestion and from the respiratory tract following inhalation which makes it a dangerous chemical to be used as preservative [8]. **Pandey et al.**.[2] stated that ingestion of formalin can lead to immediate deleterious effects on almost all system of the body including gastrointestinal tract, central nervous system, cardiovascular system, hepato-renal system causing gastrointestinal hemorrhage, cardiovascular collapse, convulsions, sever metabolic acidosis and acute respiratory distress syndrome [2] . **Tong et al.** [9] also reported that acute and chronic inhaled formalin has been demonstrated to associated with various toxic effects including hepatotoxicity, neurotoxicity, reproductive toxicity, respiratory toxicity and cancer in epidemiological and animal studies. Exposure to formaldehyde have been demonstrated to lead to an increase in lipid peroxidation products in different tissues [10]. Formaldehyde can be used in a variety of industries, including the medical, detergent, cosmetic, food, rubber, fertilizer, metal, wood, leather, petroleum, and agricultural industries [11]. According to the statement of **WHO** [6] many products containing formaldehyde as adhesives and glues, cosmetic goods, deodorants, detergents, soaps, paints and especially white papers, explosives, fertilizers, filters and chemicals, protective covering used in keeping foods, and in the production and tanning of leather and fur, parquets, plywood, formica, rubber, latex, eraser, polish, varnish, textile goods and water softeners. Formaldehyde is also an important public health problem, because it present in tobacco smoke, and is released from various household products such as plywood, particleboard, furniture, and carpeting and it is used in

some cleaning products [12] [13]. Furthermore, a significantly greater number of people are exposed to lower levels of formaldehyde in the environment, as it is generated by automobile engines [14]. Smoking is another important source of formaldehyde[15]. Epidemiological studies have been indicated association between formaldehyde exposure and elevated cancer risks at various sites, including the brain, nasal cavities, lung [16], pancreas [17] , lymphohematopoietic system [18] [19]. The U.S. National Toxicology Program [20] and the International Agency for Research on Cancer [21] have both classified formaldehyde as a human leukemogen based on epidemiological studies that suggest an increased risk of leukemia. A possible toxic effects of formalin on the human health and as well as laboratory animal was also reported [9] [22] [23]. The rats exposed to formaldehyde in drinking-water at doses of 1.2, 15 or 82 mg/kg of body weight per day for males and 1.8, 21 or 109 mg/kg of body weight per day for females showed an increase incidence of renal papillary necrosis in both sexes [24]. Significant elevation in blood urea concentration were observed in birds given formalin (37% formaldehyde) mixed homogeneously in the food at dose of 2.5, 5 and 10 ml/kg [25]. Superoxide dismutase, glutathione peroxidase, catalase and malondialdehyde levels in the liver tissue samples were significantly higher rats injected with 10% formaldehyde (10 mg/kg, ip) every other day for 14 day of experimental period. Also, light microscopic evaluation of liver tissue samples of formaldehyde exposed rats revealed enlarged sinusoids filled with blood, mononuclear cell infiltration in the portal areas and around the central veins,vacuolar degeneration hepatocytes, and some had a hyperchromatic nucleus. In periodic acid Schiff (PAS) stain staining tissue, the hepatocytes around the portal areas were PAS stain negative [26]. The binding of formaldehyde to proteins and nucleic acids, subsequent to being metabolized, is known as metabolic binding. Inhaled formaldehyde rapidly forms covalent bonds, through several metabolic pathways, with intracellular DNA, RNA, and protein pools, and these interactions underlay the toxic effects of formaldehyde. The direct binding reaction without metabolic breakdown, generally in nasal mucosa, is called irreversible binding and results in necrosis, allergy, and mutagenicity in living organisms [27].

Salvia officinalis L. (common sage) is a popular herb and aromatic plant belonging to family Lamiaceae comprising about 900 species. It is commonly used as a spice and condiment in food preparation, particularly in the Mediterranean cuisine [28] [29] [30]. Sage and its isolated oils are largely responsible for various therapeutic effects mainly indicated in the treatment of muscle pain and digestive disorders [31] as well as in promoting energy expenditure and fat oxidation, which may aid in body weight reduction [29]. S. officinalis has been extensively used as a medicinal plant in treating several diseases and recent studies have shown promising activity in treating cancer [32], heart disease, dementia and obesity [33]. **Karimzadeh and Farahpour** [28] reported that S. officinalis 5% were significantly promoting wound healing effect and can be considered as an appropriate compound for clinical application in wound care. Salvia officinalis also usage in traditional phytotherapy for bronchitis, cold, dental care, fever, liver, kidney and stomach ailments, midgrade depression, throat ache, women reproductive system , wounds and ulcers [34] [35]. Phytochemical analysis showed that the Salvia leaf contains tannic acid, cineole, oleic acid, ursonic acid, ursolic acid, cornsole, cornsolic acid, fumaric acid, chlorogenic acid, caffeic acid, niacin, nicotinamide, flavones, flavonoid glycosides, thujone and estrogenic substances [36]. The hydroethanolic leaf extract of S. officinalis showed the highest total flavonoid and phenolic content and antioxidant capacity [28]. Also, pharmacological and phytochemical potential of Salvia have been demonstrated by **Alberto et at.** [37]. Salvia is a medicinal plant reported to have multiple pharmacological effects including antibacterial [38] [39] [40], antiviral [41], antidiarrhea [42], anti-inflammatory [35] [43] [44], antinociceptive and antiproliferative [43], diuretic [35], immunomodulatory [45], hypoglycemic [46], fungistatic [47], antimutagenic effect [48] [49], anticancer [50] and antioxidant [51] [40] [52]. Also, several experimental studies have demonstrated the antioxidant properties of S. officinalis extract and some of its constituents [53] [54] [55]. Flavonoids and other phenolic acids from S. officinalis may contribute to its total antioxidant activity [56]. The antioxidant properties and total phenolic of different extracting solvents of thyme, sage, and marjoram were examined and the results showed that thyme, sage, and marjoram have a potential use as natural antioxidants due to their significant antioxidant activity [57]. HPLC analysis of methanolic extract revealed the presence of: rosmarenic acid, methyl rosmarenate, caffeic acid, cinnamic acid, chlorogenic acid and quinic acid as phenolic acids, besides some flavonoids such as ferulic acid, apigenin, luteolin and quercetin [58]. Broiler chickens fed diets enriched with essential oil of S. officinalis (0.05%) for 5 weeks showed elevated the total antioxidant status in plasma, significantly reduced malondialdehyde (MDA) concentrations in kidney tissues of chickens supplemented with sodium selenite [59]. **Loizzo et al.** [60] stated that S. officinalis essential oil inhibited renal adenocarcinoma cell growth [61]. **Koubaa et al.** [62] suggest that the essential oil of S. officinalis might play a role in reducing the toxic effect of vanadium whereas Co-administration of essential oil of S. officinalis for 10 days induced decrease in the levels of serum renal markers (creatinine, urea, blood urea nitrogen , lactate dehydrogenase, alkaline phosphatase activities and lipid peroxidation thiobarbituric acid reactive substances and protein carbonyl) and increased the endogenous antioxidants levels in male rats intoxicated with vanadium (it has toxicological effects and pro-neoplastic action that affects many organs, specially the kidney), also administration of S. officinalis essential

oil minimized histopathological changes induced by vanadium in rat kidney was observed. Oral administration of methanolic extract S. officinalis at dose of 100 and 150 mg/kg bw for 7 days before the administration of a single intraperitoneal dose of cyclophosphamide showed significant restoration in the malondialdehyde (MDA) and a significant increase in superoxide dismutase (SOD) and catalase (CAT) activity in in liver, kidney, and heart tissues of cyclophosphamide -treated rats as compared to cyclophosphamide only treated group [63]. Administration of 250 and 500mg /Kg bw of S. officinalis potentially protect the damages in liver of mice caused by acetaminophen. In addition, they considerably improve the tissue damage and the biochemical indices in the liver damages [64]. Treatment with the low dose of sage methanol extract (100 mg kg bw) for five weeks increased the plasma levels of the anti- inflammatory cytokines IL-2, IL-4 and IL-10 and reduced the plasma level of the pro- inflammatory cytokines IL-12, TNF- , and KC/GRO in mice [65]. Oral intubation of alcoholic extract of S. officinalis leaves (150 mg/kg bw) daily for 45 days revealed beneficial effect against deleterious effect of acrylamide (1 mg/kg bw in drinking water) and significantly increase serum albumin and globulin concentration in male rats, as well elevation in serum GSH and depression in peroxynitrite radical concentration were observed [66]. Sage constituents with their antioxidant properties overcame the lower in the total protein content perhaps by preventing oxidative stress and protein fragmentation and enhancing protein synthesis [67]. Besides, cytogenetic effect of plant may be due to its ability to act as free radicals scavenger so it can captures reactive oxygen species (ROS) release from toxic substance like acrylamide [68].

Herbal medicine is a complementary therapy that uses plants to treat disorders. In various countries throughout the world, a large number of plants have been used as therapeutic agents in the traditional medicine [69]. There is also an emerging increase in the consumption of herbal formulations by the public because of the strong belief that these products are natural; hence, they are safe for the treatment of ailments [70]. Majority of the present day diseases are due to the shift in the balance of the pro-oxidant and the antioxidant homeostatic phenomenon in the body. The antioxidant defense systems can only protect the body when the amount of free radicals are within the normal physiological level; but when this balance is shifted towards more of free radicals, it leads to oxidative stress which may result in tissue injury and subsequent diseases [71]. Antioxidants can inhibit or delay oxidative chain reactions in lipids, proteins, carbohydrates, and DNA [72]. Several studies have proposed that natural antioxidants may be less toxic effect of free radicals [73]. A review of the literature revealed that Salvia officinalis is known by utilization as a medicinal plant in different countries for a variety of medical purposes and sage is reputed to be one of the richest sources of potent antioxidant [74].

The kidney is a vital organ, which plays an essential role in health, disease and overall development and growth. The main function of kidney is to maintain total body fluid volume, its composition and acid base balance [75] [76] [77]. The kidney is a common target for toxic xenobiotics due to its capacity to extract and concentrate toxic substances by highly specialized cells and also, due to its large blood flow [78]**.** Herbal medicine is a complementary therapy that uses plants to treat disorders. In various countries throughout the world, a large number of plants have been used as therapeutic agents in the traditional medicine [69]. There for the present work aimed to study the possible nephroprotective role of aqueous extracts of S. officinalis leaves as used in traditional medicine in Libya according to the doses recommended in the popular treatment and herbalist on histological alterations of kidney in animal model intoxicated with formalin.

II. Material and Methods

Experimental animals and treatment

Healthy adult male Swiss albino mice (Mus-musculus) 8 to 10 weeks old and weighing 24 -30 gm were obtained from the Animal Breeding House of faculty of veterinary medicine, Omar Al mukhtar University, Al Bayda-Libya . They were housed in the laboratory animal room in clean plastic cages (15 mice/ cage) under controlled conditions of temperature (22 ± 3)°C and photoperiod (12h light: 12h dark) cycle. The animals were maintained on standard commercial pellet diet and clear drinking water ad libitum. The mice were acclimatized for a week prior to the start of experiments. The mice were divided equally into 4 equal groups of 15 mice each and subjected to the following treatments .The first group was received only standard diet and clear drinking water and considered as control group, the second group was given orally by oral gavage 0.1 ml aqueous extract of S. officinalis at dose level 120 mg/kg bw once per day for 3 successive weeks, third group was received formalin at dose level 2.4ml/kg body weight in drinking water for 3 successive weeks (Doses were estimated based on default drinking water intake values for mice), and the fourth group was received the same dose of both formalin along with aqueous extract of S. officinalis by the same manner and for the same period.

Material used:

Fresh plant was collected from Zawyet Alargob region west of Al Bayda city in Al-Jabel Alakhder (Libya). The plant was authenticated in faculty of Pharmacy, Omar mukhtar university, Al Bayda-Libya. The plants were cleaned and used to prepare aqueous extract of the plant as used in traditional medicine.

Preparation of the aqueous extracts of salvia officinalis :

leaves of Salvia officinalis L were air-dried and extracted by added 50ml of boiling water to 1.5g of drying leaves then leave it to cool. Extract water was given by oral gavage with dose equivalent to traditional dose use (120 mg/kg)[79]**.**

Formalin (formaldehyde) 37% was purchased from (Sigma Co,Germany). Mice were given formalin in drinking as 2.4ml/kg for 3 weeks. Formalin was chosen because it has been reported to induce hematopoietic toxicity ,leukemia, liver necrosis and cancer [80] [81] [82] [83] [84]. Doses were estimated based on default drinking water intake values for mice.

Histopathological study :

At the end of the experimental period (on days 22 post-treatment), the animals from both control and experimental groups were dissected after sacrificed by cervical dislocation without anesthesia (A minimum of 6 animals from each group were necropsied to evaluate pathological lesions . For the light microscopic examination the kidney samples were collected from both control and experimental animals and cut into small pieces of approximately 3-5 mm size and immediately fixed in aqueous Bouin's fixative for 24 hours, then washed in running tap water, dehydrated in ascending grades of ethyl alcohol , cleared in xylol, impregnated in paraffin wax (melting point between 56°C and 58°C), sectioned with rotary microtome (Leica RM 2125) at 5 µm thicknesses and stained with Harri's Hematoxylin and Eosin according to **Bancroft and Gamble**[85]. Stained sections were examined under light microscope and histopathological changes were recognized and photographed using Nikon Eclipse E400, Japan with camera head.

III. Results:

Kidney sections from the control group showed intact histological structure of glomeruli and renal tubules. Also, normal feature of the tubules in medulla region was observed (Figs.1-3). There were no detectable histopathological lesions in kidney sections of mice treated only with aqueous extract of S. officinalis for 21 days whereas the kidney histological sections of those animals showed regular structure with well distributed glomeruli and related tubules (Fig.4). In contrast, the opposite situation was found in the kidney sections of mice treated with formalin were detected in glomeruli and in convoluted tubules (Fig.5-9) compared to those of control group. The main characteristic abnormalities were the appearance of vacuolization and swelling the lining epithelium of tubules, inflammatory cells infiltration and hemorrhage in the interstitial tissue, necrotic or desquamation lining epithelium in the luminal tubules, intratubular esinophilic casts in some renal tubules and such alteration were more prominent in proximal convoluted tubules. Beside that renal corpuscles with completely obscured or stenosis urinary space were frequently observed and also shrinkage glomeruli of some renal corpuscles with widening urinary space, many glomeruli appeared with less cellularily , dilation and congestion blood vessels with hemolysis blood were seen. While, administrated of aqueous extract of *S. officinalis* along with formalin induced marked improvement in the histological structure of kidney in comparison to formalin only treated group, whereas the severity of the above cited histological abnormalities ranged from mild to moderate degree (Figs.10 and 11).

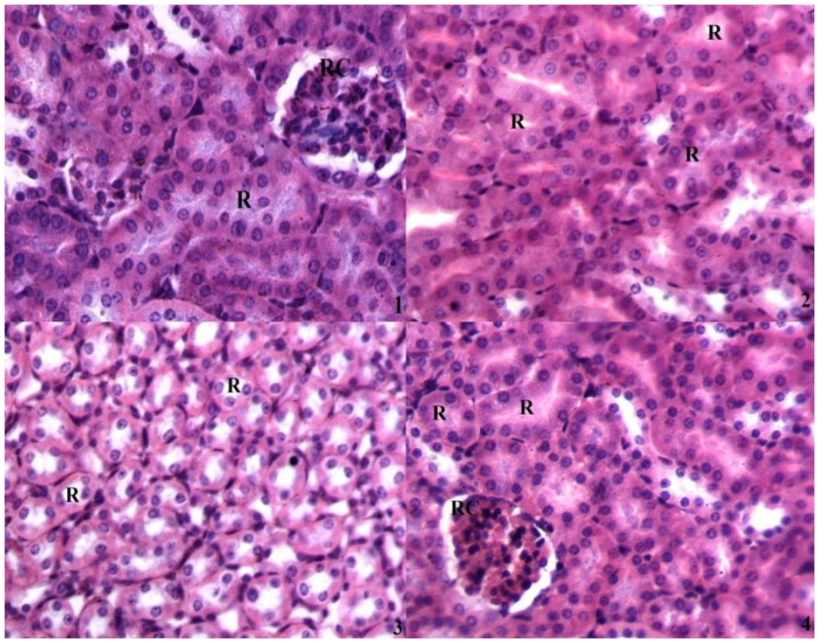

Fig.(1):A section of kidney of mouse from control group showing renal cortex with normal architecture of renal tubules (R) and renal corpuscles (RC) (H&E stain,X400). Fig.(2): A section of kidney of mouse from control group showing normal feature of lining epithelium of renal tubules (R) in cortex region (H&E stain,X400). Fig.(3): A section of kidney of mouse from control group showing normal feature of renal tubules (R) in the medulla region (H&E stain,X400). Fig.(4): A section of renal cortex of mouse treated with aqueous extract of *S .officinalis* leaves showing normal feature of renal tubules (R) and renal corpuscles (RC) (H&E stain,X400).

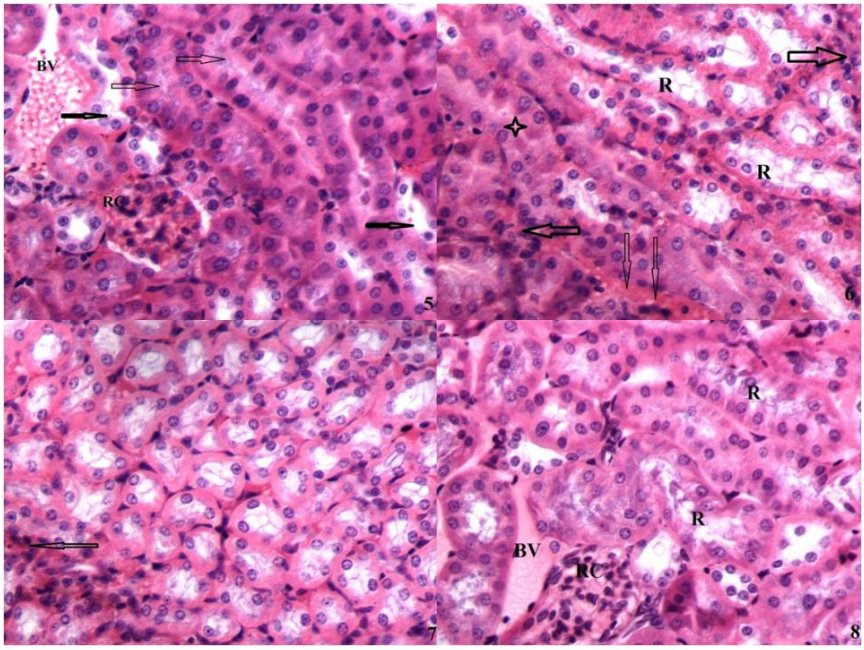

Fig.(5): A section of renal cortex of mouse treated with formalin in drinking water for 3 successive weeks showing renal tubules with swelling lining epithelium and occlusion lumen(Arrows), note also degeneration renal tubules with necrotic or desquamation lining epithelium and debris in the lumen of renal tubules (Thick Arrows), Renal corpuscles (RC) with stenosis urinary space and glomerulus appear with congested capillaries of glomerular tuft and less cellularily, Dilation and congestion blood vessel (BV) (H&E stain,X400). Fig.(6): A section of renal cortex of mouse treated with formalin in drinking water for 3 successive weeks showing degeneration and necrotic renal tubules (R) with vacuolated swelling lining epithelium, note also renal tubule with occlusion lumen (Star), Inflammatory cells infiltration (Thick Arrows) and hemorrhage in interstitial tissue (Thin Arrows) (H&E stain,X400). Fig.(7): A section of renal medulla of mouse treated with

formalin in drinking water for 3 successive weeks showing focal accumulation of inflammatory cells infiltration in the interstitial tissue (Arrow) (H&E stain, x400). Fig.(8): A section of renal medulla of mouse treated with formalin in drinking water for 3 successive weeks showing renal corpuscles (RC) with completely occlusion urinary space and glomerulus appear with less cellularily, Degenerated renal tubules (R), Congested blood vessel (BV) (H&E stain,X400).

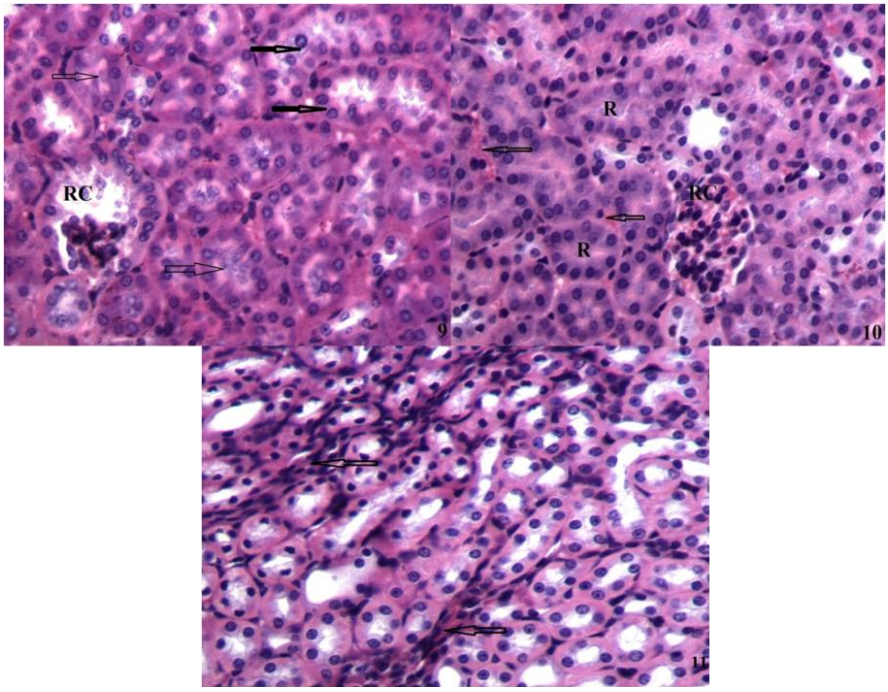

Fig.(9): A section of renal medulla of mouse treated with formalin in drinking water for 3 successive weeks showing degeneration of renal tubules with necrotic lining epithelium (Thick Arrows), note also the intratubular casts (Arrows), Renal corpuscles (RC) with shrinkage glomerulus and widening urinary space (H&E stain, x400). Fig.(10): A section of renal cortex of mouse treated with formalin and aqueous extract of *S. officinalis* leaves showing an improvement in the renal tubules (R) and renal corpuscles (RC), Interstitial hemorrhage(Arrows) (H&E stain, x400). Fig.(11): A section of kidney of mouse treated with formalin and aqueous extract of *S. officinalis* showing cortex and medulla region with normal feature with slight increase inflammatory cells infiltration interstitial tissue (Arrows) (H&E stain, x400).

Discussion:

The kidney is the target of many xenobiotics toxicants. There are many factors that contribute to the sensitivity of the kidney via, presence of variety of metabolizing enzymes and xenobiotic transporters, large blood flow and concentration of solutes during urine production. Further physiological, anatomical, and biochemical features of the kidney make it particularly sensitive to many toxins and drugs [86]. Present investigation was carried out with the aim of evaluating the possible role of *S. officinalis* in modulating the in vivo toxicity and oxidative renal injury of formalin consumption. In the present research no detectable histopathological lesions in kidney sections of mice treated only with aqueous extract of *S. officinalis*. While, many histopathological lesions in glomeruli and in convoluted tubules were detected in formalin only treated group. Exposure to formaldehyde has been demonstrated to lead to an increase in lipid peroxidation products in different tissues [10].The glomerulus is the initial site of exposure to chemicals in the nephron, and various nephrotoxic substances produce lesions on this location. In some cases, the chemical change glomerular permeability to proteins by altering the size and charge-selective functions. Circulating immune complexes can be trapped within the glomerulus which may result in complement activation, attraction of neutrophils and phagocytosis. Neutrophils and macrophages are commonly seen in the glomerulus in membranous glomerulonephritis, and the local release of cytokines and reactive oxygen species may contribute to glomerular injury [87]. Also, formalin lead to renal injuries was demonstrated by other investigators, since formalin nephrotoxicity is characterized functionally by

significant increase in blood urea concentration in birds fed higher formalin levels 2.5, 5, and 10 ml/kg mixed homogeneously in the food [25]. Also, formalin nephrotoxicity is characterized morphologically by increased incidence of renal papillary necrosis in male and female rats exposed to formaldehyde in drinking-water [24]. Numerous studies have demonstrated that ROS such as superoxide, hydroxyl radical anion, and hydrogen peroxide are important mediators of DNA damage and tissue injury [88]. Furthermore, formaldehyde causes cytotoxicity through the formation of strong DNA–protein cross-links, as well as cross-links with other molecules, e.g., amino acids [89] [90] [91]. Formaldehyde was observed to affect cerebral oxidant/antioxidant systems and cause oxidative damage. Moreover, excessive production and accumulation of reactive oxygen species (ROS) can become hazardous to cells and tissues [92] [90] [93] [94]. **Songur *et al.*** [95] observed that exposure to formaldehyde during the adult period (10 mg/kg, 10 days, ip) caused an increase in oxidant substances, such as malondialdehyde (MDA), but resulted in a decrease in the activity of antioxidant enzymesin the rat. In another study, it was found that exposure to formaldehyde (10 mg/kg, 14 days, ip*)* led to an increase in the MDA level and a decrease in the activity of SOD and GSHPx in the rat prefrontal cortex[96]. ROS are important mediators of cellular injury, play a role in oxidative stress, and can contribute to a variety of diseases, or be present in situations where toxicity is produced. ROS-initiated oxidative stress can be regulated by cellular defense mechanisms, including superoxide dismutase (SOD*)*, catalase (CAT*)*, and glutathione peroxidase (GSH-Px) [97]. It has been also reported that formalin change the cellular glutathione (GSH) status and generates oxidative free radicals [10] [98].

Whereas GSH content is an important naturally occurring antioxidant, which prevents free radical damaging effects and helps in detoxification process by conjugating with chemicals. In addition, GSH is central to the cellular antioxidant defenses and acts as an essential cofactor for antioxidant enzymes including glutathione peroxidase (GPx), glutathione-S-transferase [99]. The above mention data may explain the mechanism by which formalin occurs sever histopathological alterations. In the present study no abnormalties in kidney of mice treated with aqueous extract of *S. officinalis* only. Also, Normal histological structure of renal parenchyma from cortex and medulla were observed in Kidneys of mice treated with *S. officinalis* either with (0.3g/kg bw) or (0.6g/kg bw) for two weeks[100]. Our result is also demonstrated that Co-administration of aqueous extract of *S. officinalis* along with formalin showed marked improvement in the histological structure of kidney in comparison to formalin only treated group. Whereas, the histological abnormalities ranged from mild to moderate degree. Our findings are consistent with **Ahmed *et al.*** [100] who noticed that treatment with sage (*Salvia officinalis* L. at dose level 0.3 or 0.6 g/kg bw) for two weeks exhibited a protection against cyclophosphamide induced different histopathological lesions in kidneys, liver and testes in mice. Sage (*Salvia officinalis* L.) has been proposed as effective against cardiovascular diseases, brain and nervous disorders, various infections (such as throat infections, dental abscesses, and mouth ulcers) and digestion problems. Polyphenolic compounds (phenolic acids, polyphenols, flavonoids, phenolic terpenes) that lead to antioxidative potential could be responsible for these health benefits of sage products [101]. **Alkan *et al.*** [63] suggest that oral administration of *S. officinalis* methanolic extract (50, 100, and 150 mg/kg body weight) for 7 days before the administration of a single intraperitoneal dose of cyclophosphamide (40 mg/kg bw) has a protective effect against cyclophosphamide induced oxidative stress and genotoxicity through its antioxidant property. **Nagy *et al.*** [102] analyzed the phenolic components in dried spices and found that rosmarinic acid was one of the main constituents in the methanolic extracts of oregano, sage and thyme, which was consistent with other research. Rosmarinic acid and hydroxycinnamic acid compounds have been demonstrated to possess strong antioxidant activity [103]. **Alshubaily and Jambi** [104] concluded that the biological activity of sage water extract (1ml/Kg bw) could be attributed to the presence of the essential oil, phenolic contents and other antioxidant components. These antioxidant compounds have the ability to stimulate endogenous antioxidant defense systems and scavenge reactive species [105]. The leaves of *S. officinalis* possess some therapeutic effects due to the presence of mainly flavonoids; phenolic compounds such as carnosic, rosmarinic, caffeic, and salvianolic acids; and other phenolic structure-based compounds [106] [107]. Through their free radical scavenging capacity, *S. officinalis* and its phenolic compounds have been shown to have protective effects against oxidative stress [55]. In the present study treatment with *S. officinalis* may be prevent oxidative stress and enhance the

antioxidant defense system in kidney of mice intoxicated with formalin. This finding goes parallel with the results of various authors who reported that the leaves of *S. officinalis* L. (sage) are well known for their antioxidative properties [106] [108] [109]. It has been reported that the main antioxidant activity of *S. officinalis* is attributed mainly to rosmarinic acid and the diterpene phenolics carnosol and carnosic acid [110]. Rosmarinic acid and hydroxycinnamic acid compounds have been demonstrated to possess strong antioxidant activity [103]. In this respect **Koubaa *et al.*** [62] suggest that *S. officinalis* might play a role in reducing the toxic effect of vanadium whereas Co-administration of essential oil of *S. officinalis* for 10 days induced decrease in the levels of serum renal markers (creatinine, urea, blood urea nitrogen and lipid peroxidation) and increased the endogenous antioxidants levels in male rats intoxicated with vanadium (it has toxicological effects specially the kidney), furthermore minimized histopathological changes induced by vanadium in rat kidney was observed.The protective effect of *S. officinalis* may be also explain by **Alkan *et al.*** [63] who reported that oral administration of methanolic extract *S. officinalis* at dose of 100 and 150 mg/kg bw for 7 days before the administration of a single intraperitoneal dose of cyclophosphamide showed significant restoration in the malondialdehyde (MDA) and a significant increase in superoxide dismutase (SOD) and catalase (CAT) activity in in liver, kidney, and heart tissues of cyclophosphamide treated rats as compared to cyclophosphamide only treated group. Also, **Foruozandeh *et al.*** [64] stated that administration of 250 and 500mg /Kg bw of *S. officinalis* potentially protect the liver and induced considerably improve the liver tissue of mice administrated with acetaminophen. **Ashour *et al.*** [111] stated that oral administration ethanolic extracts of *S. officinalis* (50 mg/ kg bw) six days/week for 4 weeks to albino rats could prevent pesticides (chlorpyrifos and methomyl) induced renal toxicity *via* attenuation of oxidative stress and enhancement of the antioxidant defense system.

According to the findings of this study, it can be concluded that administration of formalin for 21 days can lead to renal disorder in mice. The Co- administration of aqueous extract of *S. officinalis* leaves with formalin partially resulted in decreased of renal injuries caused by formalin exposure.

Conclusion :

It is concluded that treatment with formalin for a 3 week has harmful effects on the renal tissue of mice and consumption of aqueous extract of *Salvia officinalis* succeed to lessen formalin stress induced renal cellular injury in mice and over long exposure to formalin may continually possess potential hazards to the human health. The improvement in the histopathological findings may related to the antioxidant activities of this plant and may provide a useful approach in attenuating the renal injury.

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