

**EXPERIMENTAL EVALUATIONS OF THE NEPHROPROTECTIVE PROPERTIES
OF GINGER (*ZINGIBER OFFICINALE*), CINNAMOMUM VERUM AND *NIGELLA
SATIVA* IN STZ INDUCED DIABETIC RATS**

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Received 4th May 2017; Revised 11th May 2017; Accepted 16th May 2017; Available online 1st June 2017

ABSTRACT

Diabetes mellitus (DM) is a heterogeneous disease, characterized by chronic hyperglycemia caused by defects in insulin secretion, insulin action, or both, resulting in problems in the metabolism and functions of carbohydrate, lipid, and protein.

The objective of the present work was to investigate the Anti-hyperglycemic, antihyperlipidemic and reno-protective effects of Ginger (*Zingiber officinale*), *Cinnamomum verum* and *Nigella Sativa* in Streptozotocin-diabetic rats.

The study was conducted from September 2016 to April 2017. In this study, rats were divided into 8 groups according to treatment regimen. Each group comprised of 5 rats. After animal sacrifice histopathological examination of kidney and pancreas was done.

Histopathological examinations of kidney and pancreas showed a moderate protection of renal glomeruli and tubules, and mild protection of pancreatic cells depending on the treatment either before or after induction of diabetes. *Cinnamomum verum* was found to be the best in treatment and protection of nephropathy.

**Keywords: Diabetes Mellitus, *Zingiber Officinale*, *Cinnamomum Verum*, *Nigella Sativa*,
Nephroprotection**

INTRODUCTION

Diabetes mellitus (DM), is a group of metabolic disorders which results in high blood sugar levels over a long period [1]. Diabetes is a chronic metabolic disorder which has been in existence since long high and affects about 4-5% of the population worldwide [2]. The number of people suffering from Diabetes Mellitus is globally increasing daily with an estimated 366 million people will be, affected by the year 2030 against 191 million estimated in 2000 [3]. Diabetes patients are exposed to some long-term complications like nephropathy, retinopathy and neuropathy [4]. Diabetic nephropathy is characterized by alterations in both glomerular and tubular structure and function. The pathogenesis of diabetic nephropathy includes genetic, hemodynamic and metabolic factors, and oxidative stress, as well as renal hypertrophy, but the exact mechanism is not clear [5,6].

Despite the availability of medication for diabetes, traditional remedies are desirable and are currently being investigated. Clinical research has confirmed the efficacy of several plant extracts in the amelioration of diabetic disorders. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Ginger (*Zingiber officinale* Roscoe, Zingiberaceae)

is widely used around the world in foods as a spice. Since ancient times, it is being used in Chinese, Ayurvedic and Tibb-Unani herbal medicines for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes [7,8,9]. Ginger rhizomes are widely used in foods for their nutritional and medicinal benefits, especially in Asia [10]; for example, as a source of Fe and Ca for women during the post-natal period and also for treating morning sickness and other gastrointestinal disorders [11]. More recently, ginger juice was found to have antidiabetic effect in alloxan-induced diabetic rats [10]. In a similar study, ginger juice was reported to cause significant reduction in the fasting glucose levels and an increase in the insulin levels in streptozotocin (STZ)-induced type 1 diabetic rats [12]. Al-Amin *et al* also found that ginger possesses hypoglycaemic, hypocholesterolaemic and hypolipidaemic potential. They observed, in addition to that raw ginger was effective in reversing proteinuria in diabetic rats [13]. Studies on the hypoglycaemic properties of ginger in animals have reported variable results [13,14,15] and there has been no report on the effect of ginger extract on the selected glycolytic enzymes involved in carbohydrate metabolism.

Cinnamomum verum belongs to family Lauraceae, widely used as spices and food preservatives in form of oils and extracts [16]. This traditional plant is extensively used for the treatment of different kidney ailment and due to the sweet bark of plant, it is known as sweet wood [17]. The plant may have protective role in alleviating the sign and symptoms of many diseases due to oxidative stress [18]. The plant has also been used for the treatment of several diseases [19]. Recently, active water-soluble components were isolated and found to mediate beneficial effects on glucose metabolism [20-22]. These components were identified as polyphenols, also named procyanidins, which usually occur as oligomers of epicatechin and the flavonoid catechin [21]. In a previous study on the hypoglycemic effect of cinnamon extracts on mice, it was found that extracts isolated from two species of the genus *Cinnamomum*, exerted different anti-diabetic pharmacological effects, which improved not only the insulin sensitivity but also the pancreatic β -cell function in mice [23]. Other study confirmed that a one trimerprocyanidin oligomer isolated from cinnamon extract, cinnamtannin D-1, protected pancreatic β -cells from lipotoxicity [24].

Nigella Sativa belongs to family Ranunculaceae. It is an annual, herb, 30-40

cm high. Seeds of *N. sativa* are commonly known as kalonji has a long history of use in folk medicine as a diuretic and hypotensive agent. The essential oil of *N. sativa* seed has an antioxidant property that makes it useful in treating cardiovascular disorders [25]. It has been found that intraperitoneal administration of *N. sativa* (thymoquinone) significantly decreases hyperglycemia in STZ-induced diabetes mellitus in the rats [26]. The therapeutic effect of *N. sativa* is related to the presence of many active components isolated from seeds and its oil including thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine, and alpha-hederin [27] and flavonoids [28].

HPLC fingerprint is a technique used for characterization and authentication of herbal drugs. The main objective was to determine the chromatograms of standard medicinal plant samples by High Performance Liquid Chromatography (HPLC). These HPLC fingerprints of standard samples could be used as benchmarks for the comparison when doing the qualitative and quantitative analysis of unknown samples [29, 30].

MATERIALS AND METHODS

This study was conducted in the department of Clinical Pharmacy, College of Pharmacy, Northern Border University,

Rafha Campus, and department of anatomy, faculty of medicine, King Abdul Aziz University, Jeddah, from September 2016 to April 2017.

Animals:

Forty (40) healthy and active adult albino male rats, 90-120 days old, and weighing from 200-240 gm were selected. Rats were acclimatized under environmental condition with $24 \pm 3^{\circ}\text{C}$, 12hr light/dark cycle and good ventilation.

Induction of Diabetes:

The rats were made to fast overnight before the induction of diabetes by a single intraperitoneal injection of 60 mg/kg STZ freshly dissolved in distilled water [31]. Hyperglycemia was confirmed 4 days after injection by measuring the tail vein blood glucose level with an Accu-Check Sensor Comfort glucometer. Only the animals with fasting blood glucose levels ≥ 250 mg/dl were selected for the study.

Experimental Design:

Following acclimatization for one week before use, the animals were randomly divided into eight groups each included 5 rats and labeled as A, B, C, D, E, F, G and H, according to the treatment.

Ginger, Nigella Sativa oil and Cinnamon were obtained from the local market. These substances were mixed with the diet, in dose of 6 gm/100 gm (6%) of diet.

Animals were divided into eight groups, Group A animals were considered as control, Group B animals were made diabetic without treatment, Group C was treated with ginger before induction of diabetes, Group D was given *Nigella Sativa* prior to diabetes induction. Group E animals were given cinnamon before streptozotocin injection, Group F, G, H animals were treated with Ginger, Nigella Sativa, and Cinnamon respectively, after diabetes induction.

Histopathological examination:

The treatment was continued for eight weeks, all groups were sacrificed in the day 57th, after that renal and pancreatic tissue were collected in 10% formalin and prepared for tissue processing, Histopathological examination was performed at department of anatomy, faculty of medicine, King Abdulaziz university, Jeddah, Saudi Arabia.

HPLC Profile:

The extracts for Ginger, Nigella Sativa and Cinnamon were diluted and filtered with HPLC grade methanol. Chromatographic analysis was carried out on a 250mm* 4.6 mm, 5 μm , 100 \AA RP-18 column. The mobile phase consisted of two solvents: Methanol (A) and water-formic acid (2%) (B). The flow rate was 1.4ml/min and the injection volume 8 μL by Hamilton microliter syringe. Spectral data from all

peaks were accumulated in the range of 200–400 nm. The analysis was carried out in a Waters® 2545 Quaternary Gradient Module pump and equipped with Waters® 2998 diode array detector using Empower 3 Software.

The mobile phase gradient elution used in the two methods was as follows:

Method A

The gradient program was begun with 30 % A and was held at this concentration for the first 5 minutes. This was followed by increased to 100 % for the next 15 minutes and held for 10 minutes then reduced to 30 % again for the following 5 minutes.

Method B

The gradient program was begun with 20 % A and was held at this concentration for the first 5 minutes. This was followed by increased to 100 % for the next 15 minutes and held for 10 minutes then reduced to 20 % again for the following 5 minutes.

RESULTS:

Histopathology of Kidney:

Section from rat kidney studied under H&E stain after sacrificing of animals showed that group D (treated with with *Nigella Sativa* before induction of diabetes), there was a moderate protection of renal glomeruli, and tubules were still dilated with damaged cell lines and luminal casts fig.1. Group G (treated with *nigella sativa*) after induction of diabetes, revealed less

protection from both glomerular changes, distal tubule showed dilated lumina and vacuolar degeneration fig2. Sections from group C (treated with ginger before diabetes) appeared with moderate protection of renal tubules, and good protection to glomerular capillaries fig.3. group F showed mild improvement in both tubules and glomerulus fig.4

Histopathology of Pancreas:

Sections from rat pancreas studied under H&E stain after sacrificing of animals in the control group A showed normal cell population and sinusoids fig.5. Group B showed cell clumping and degeneration, with vacuolation fig.6. In Group E there was preservation of normal structure and cell population fig.7. Group H showed a marked protection of pancreatic cells fig.8. When treated with ginger before induction of diabetes, Group C islets still showed vacuolated cells, others clumped and degenerated fig.9. In group F there was a marked preservation of normal structure fig.10. In group D the islets showed normal healthy cell population and dilated capillaries fig. 11, while in group G that treated with *nigella sativa* after diabetes induction there was a moderate protection and still few cell population, vacuolated and degenerated cells fig.12.

HPLC Finger Prints:

In cinnamon extract chromatogram using method A, the major peaks appeared at 1.5, 1.9, 2.2, 2.6, 3.5, 16, 24, 24.5, 24.8 and 25.5 minutes, and small peaks were obtained at 2.5, 14.5, 19, 23 and 26.5 minutes and dwarf peaks were obtained between these minutes of run fig.13.

In Black seed extract chromatogram using method A, the major peaks appeared at 1, 1.5, 1.8, 3, 4.3, 9.5, 15 and 20 minutes, and small peaks were obtained at 2, 3, 15.5, 18 and 22 minutes and dwarf peaks were obtained between these minutes of run fig.14.

In Ginger extract chromatogram using method B, the major peaks appeared at 1, 1.5, 20, 20.5, 20.8, 21.2 and 22 minutes, and small peaks were obtained at 2, 2.5, 3, 15.2, 18, 19.8 and 21.8 minutes and dwarf peaks were obtained between these minutes of run fig.15.

DISCUSSION:

The histological sections of the control animal's kidney, showed typical normal features, with normal size renal corpuscle and cellularity of glomerular capillaries, and renal tubules with intact epithelial lining. Our study results are in conformity with Shaikh Hussain *et al*, [32]. The H & E sections of STZ induced diabetes animals renal parenchyma showed hypertrophied renal corpuscle with degeneration and decreased glomerular cellularity. Renal

tubules showed damage and desquamation of lining epithelium. These results are in agreement with the study conducted by S.L TEOH *et al* [33]

Ginger in the pre-treated group showed moderate protection form renal tubule damage with marked protection from glomerular changes ,these results are almost similar to Rafieian-Kopaei M, Nasri H [34] .The renal parenchyma of the animals treated with Ginger after induction of Nephropathy showed ,moderate improvement, tubules still showed epithelial Damage and less glomerular cellularity.

Group Pre-treated with Nigella Sativa oil showed mild protection, renal tubules showed hyaline casts. Glomerular capillaries slightly shrunken ,post Diabetes ,group treated with Nigella Sativa oil showed ,mild improvement in glomerular structure, distal and collecting tubules showed marked degeneration these results are not exactly in conformity with the previous studies conducted Kanter M [35]. The difference may be due to the form ,dose and route of administration of the substance.

The group pre-treated with Cinnamon showed good protection with minimal histological changes in both glomeruli and renal tubules . The study of Mishra A has also found same protective results [36].

While the group treated after induction of STZ induced DM nephropathy showed marked improvement in both glomerular and tubular elements which even looked

more healthy than normal. These observation are in agreement with the study conducted by Mishra A et al., [37].

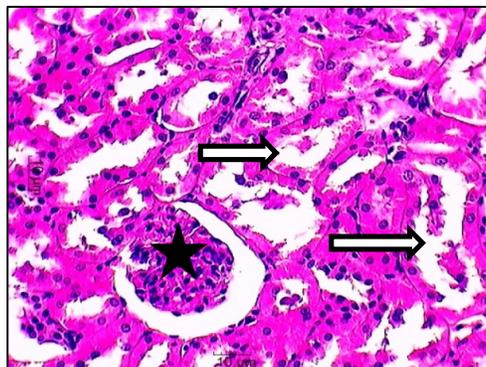


Fig.1: sections from rat kidney to show of renal tubules (arrows) and glomerular capillaries (star) of group D

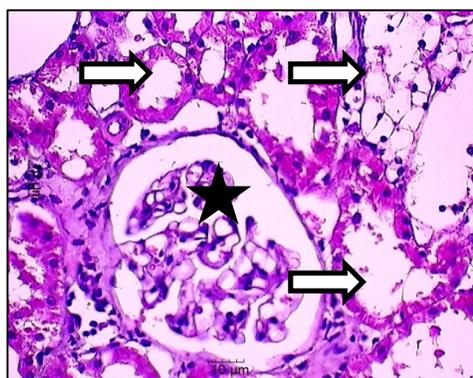


Fig.2: sections from rat kidney to show of renal tubules(arrows) and glomerular capillaries (star)of group G

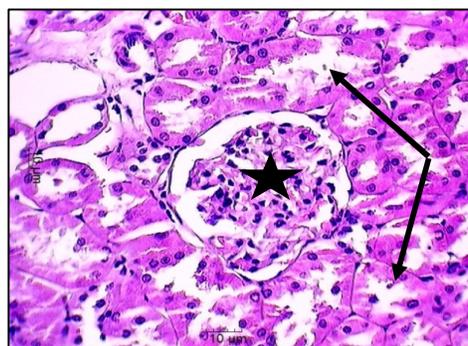


Fig.3: sections from rat kidney to show of renal tubules (arrows) and glomerular capillaries (star) of group C

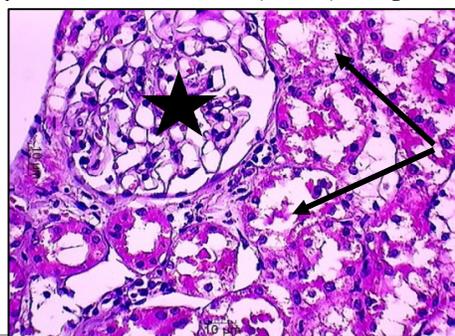


Fig.4: sections from rat kidney to show of renal tubules(arrows) and glomerular capillaries (star) of group F

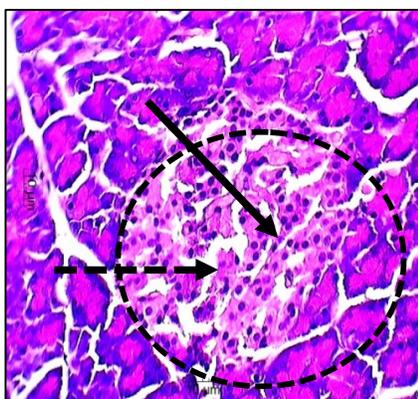


Fig.5: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows)of group A

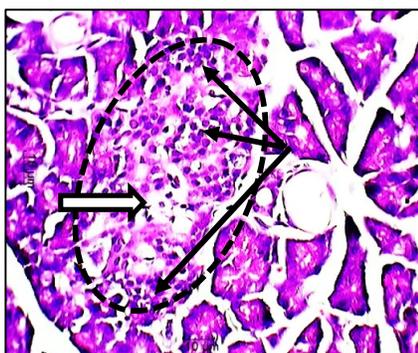


Fig.6: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group B

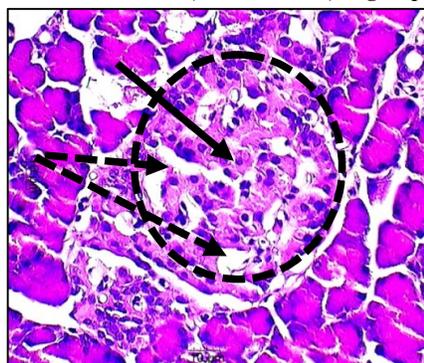


Fig.7: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group E

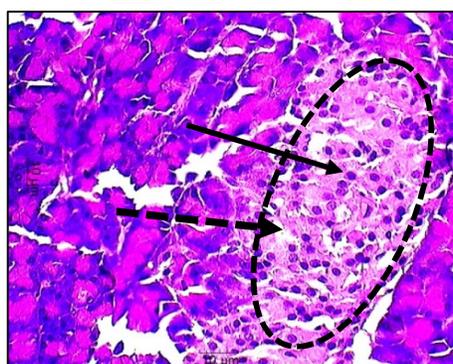


Fig.8: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group H

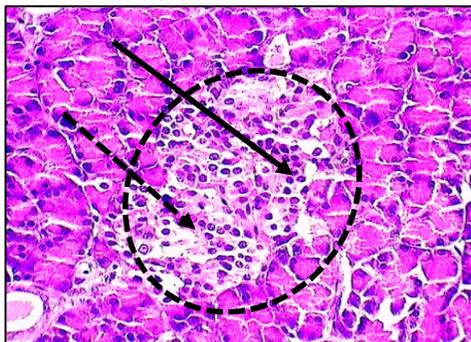


Fig.9: sections from rat pancreas to show islets of Langerhans (dotted circles). cell population (black arrows) and blood sinusoids (dotted arrows) of group C

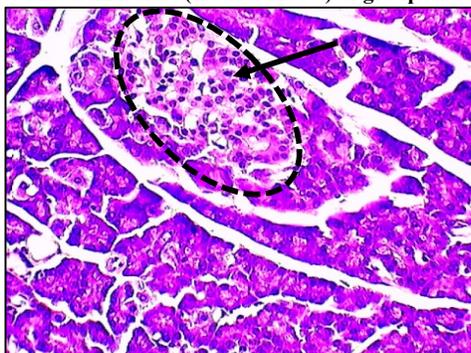


Fig.10: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group F

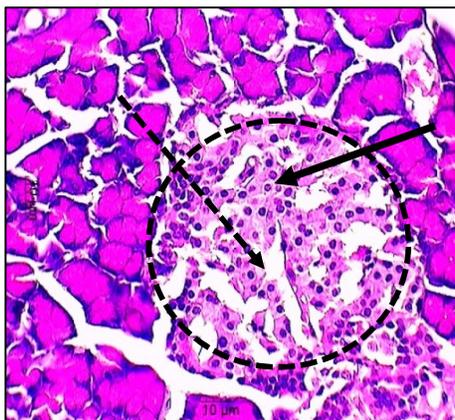


Fig.11: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group D

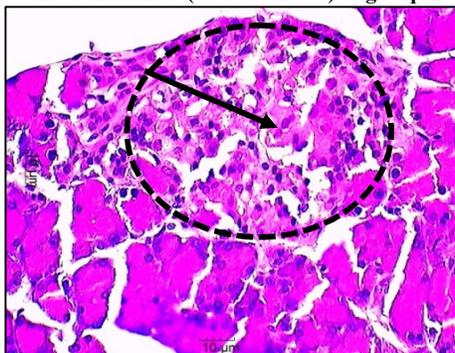


Fig.12: sections from rat pancreas to show islets of Langerhans (dotted circles) .cell population (black arrows) and blood sinusoids (dotted arrows) of group G

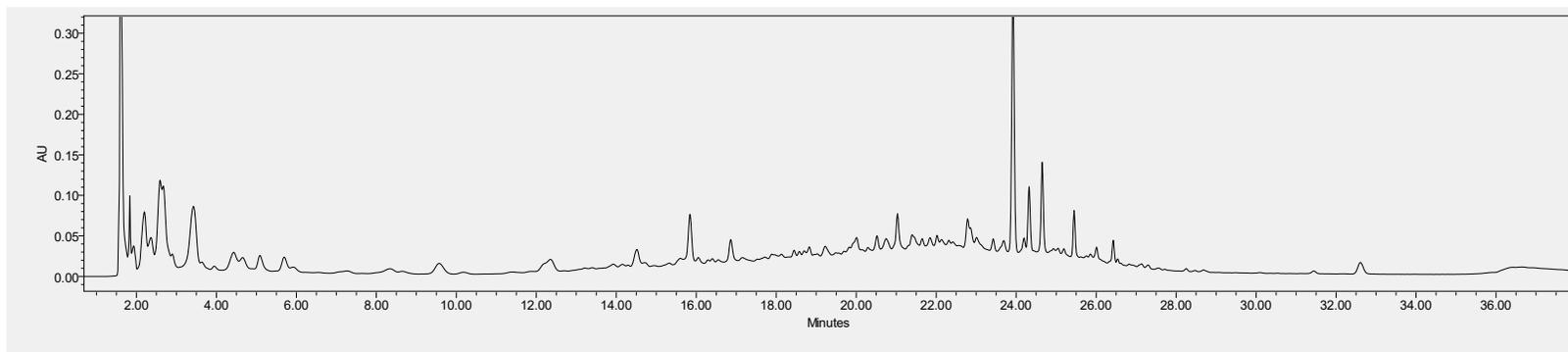


Fig.13: HPLC Fingerprints of Crude Extract of cinnamon

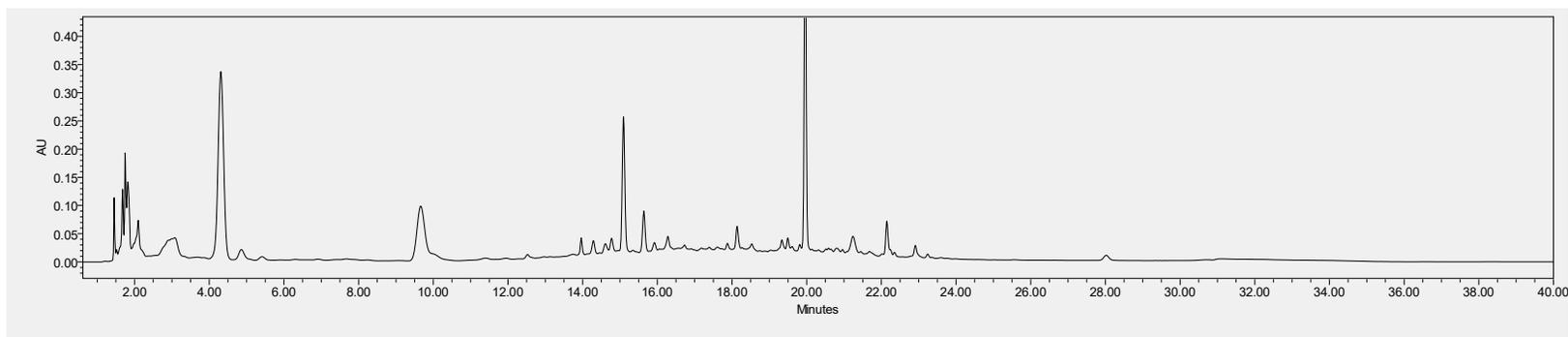


Fig.14: HPLC Fingerprints of Crude Extract of Black seed

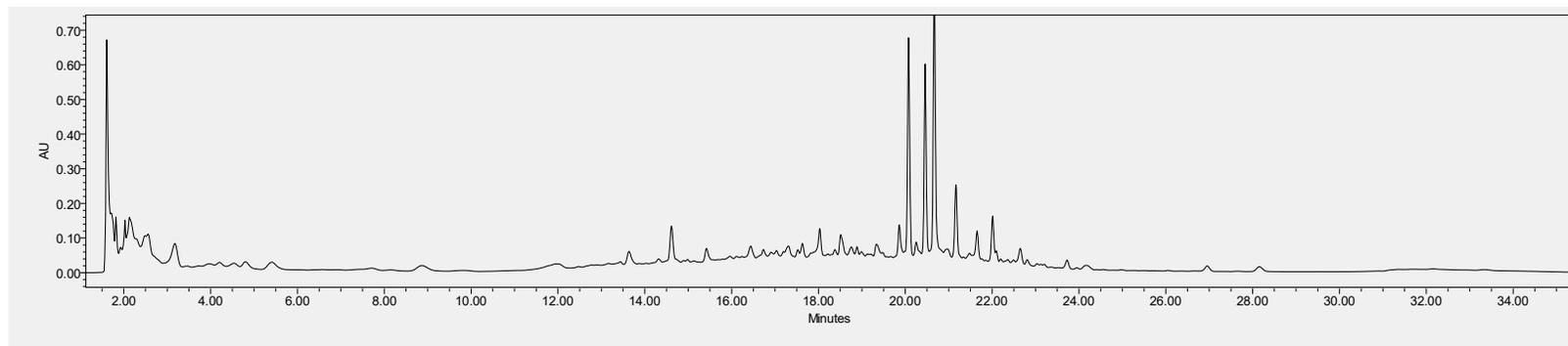


Fig.15: HPLC Fingerprints of Crude Extract of Ginger

CONCLUSION

All groups showed mild to moderate improvement or protection from diabetes induced changes. Pre administration gave better results than the already occurred Nephropathy.

The effects of Nigella Sativa Oil, Cinnamon and Ginger on Diabetes induced renal damaged are not in complete conformity with the previous studies literature which may be attributed to the dose regimen of administration, type and species of herb used or may be due the type of ingredients of the substances used in the study as the HPLC results have shown that these substances contain more than one active compounds.

High doses of antioxidants may act as pro-oxidant and may aggravate toxic effect of these substances specially Nigella Sativa.

The cinnamon showed better results in both pretreated and treated groups, in comparison to other substances used in the study. At the same time hepatotoxicity/fatty degeneration was also observed in the animals treated with Nigella Sativa. It can be concluded that Cinnamon has the potential to treat and protect the Diabetic nephropathy, therefore more studies are suggested with large sample size.

ACKNOWLEDGMENT

The research project was approved and funded by Deanship of Scientific Research,

Northern Border University, Saudi Arabia; grant NO (PHM-2016-1-6-F-5693).

Conflict of interest: None

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