ملخص مشروع رسالة ماجستير-٤

عنوان المشروع باللغة العربية	تحليل الكيمياء الحيوي لنواتج الأيض المحتملة وعوامل عصبية في شبكية العين السكري في الجرذان
English /عنوان المشروع باللغة الإنجليزية	Analysis of potential metabolites and neurotrophic factors in diabetic rat retina
Advisor /المشرف الرئيس	Professor Abdullah S. Alhomida
Minor /التخصص الدقيق للمشرف الرئيس Specification	Enzymes and Medical Biochemistry
Co-Advisor /المشرف المساعد	Dr Shams Ulola
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا	10-12 months
Abstract or synopsis of the proposal (200 words or less):	Diabetic retinopathy is being widely recognized as a neurodegenerative disease of the retina, since, retinal neurons are vulnerable to be damaged early in the disease progression. Neurotrophic factors and metabolites play an important role in the functional maintenance of neuronal cells and dysregulation has been found to cause neurodegeneration in diabetic retinopathy. In this study, We will use streptozotocin to induce diabetes in rats, then we will measure the metabolites and neurotrophic factors in serum and retinas from 3- and 12-week diabetic rats and compare those with nondiabetic rats. These investigations will identify early potential metabolites that may regulate the expression level of neurotrophic factors that cause neuronal deficits in the diabetic retina. We will utilize biochemical and HPLC analyses for metabolites assays and ELISA and immunoblotting techniques to analyze neurotrophic factor expression in the retina. These analyses will help us in establishing a link between the levels of those potential neurodegenerative metabolite(s) or factor(s) and their mechanism of neuronal damage at early stages in the disease progression. Understanding of the early neurodegenerative changes and amelioration of their levels, may be a potential therapeutic approach to combat neurodegeneration and in turn diabetic retinopathy.
Hypothesis or scientific justification of the proposal	Diabetic retinopathy is the leading cause of blindness both in the developing and

ملخص مشروع رسالة ماجستير- ٤

	developed countries. There is no treatment or prevention of diabetic retinopathy at early stage of the disease, only late stages can be treated with limited benefits. Therefore, there is an urgent research needed to better understand the mechanism of disease progression at its earliest stage before any clinical signs of retinopathy appears. Diabetes alters the metabolism both systemically and locally in several organs, including retina. We and others have found dysregulated levels of a number of neurodegenerative metabolites and neurotrophic factors in diabetic retinopathy patients and in the retina of diabetic rodents. These potential metabolites are capable of damaging the neurons. Altered levels of these metabolites are found to activate several metabolic pathways, leading to increases in oxidative stress and decreases in the level of neurotrophic factors. As a consequence, they may damage the retinal neurons in diabetic patients. However, the exact link between the levels of those potential neurodegenerative metabolite(s) or factor(s) and their mechanism of neuronal damage at early stages in the disease progression has not been established. Therefore, the hypothesis behind the proposed research is that dysregulated levels of neurodegenerative metabolite(s) and/or factor(s) in the diabetic serum and retina may induce neuronal damage; and by ameliorating their levels, neurodegeneration and in turn diabetic retinopathy can be arrested or prevented.
Specific objectives	To determine the neurodegenerative metabolites and neurotrophic factor levels in the serum and retinas from rats with streptozotocin-induced diabetes.
Methodology and Major Techniques to be used	To analyze the levels of the dysregulated metabolites/neurotrophic factors in diabetic retina, we will use rat as animal model of diabetes. Three months aged male Wistar albino rats, weighing 250–270 g will be injected single dose of streptozotocin (65 mg/kg body weight) made in citrate buffer intraperitoneally to make rats diabetic.

ملخص مشروع رسالة ماجستير-٤

	Diabetes will be confirmed after 3 days by measuring fasting blood glucose level more than 300 mg/dl. We will use eight rats (n=8) in each group; 3 and 12 weeks, control and diabetic rats. At the end of the treatments, animals will be fasted overnight and blood samples will be collected though cardiac puncture under deep anesthesia, retinas will be quickly removed, rinsed in ice-cold saline and homogenized in a cold 50 mM phosphate-buffered saline (pH 7.4) containing 1 % triton X-100, 0.2 % SDS, and a protease inhibitor cocktail by short burst of sonication. The homogenates will be then centrifuged at 10,000 rpm for 15 min at 4^{o}C. The supernatants will be separated and used for ELISA and other biochemical analyses. We will utilize biochemical and HPLC analyses for metabolites; ELISA, immunoblotting techniques to analyze neurotrophic factor expression in the retina.
Availability of Samples	Yes, We will use animal facility, College of Pharmacy, KSU for animal work after getting ethical approval for the use of animals in this project.
Availability of Chemicals	YES (•) NO ( )
Availability of Instruments	YES (•) NO ( )
Availability of Ethical Approval (if needed)	YES ( ) NO (•) Required, Yes, after Bioethical Committee approval of the use of animal, we will make rats diabetic and then will obtain retinal samples
Project Funded	YES (•) NO
Recent References	1. M. Shamsul Ola, Hosoya K, LaNoue KF (2011). Regulation of glutamate metabolism by hydrocortisone and branched chain keto acids in cultured rat retinal Müller cells (TR-MUL). *Neurochem Int.* 59(5):656-63. 2. M. Shamsul Ola, Nawaz M, Ahsan H (2011) Role of Bcl-2 family proteins and caspases in the regulation of apoptosis. *Mol Cell Biochem*. 351(1-2):41-58. 3. M. Shamsul Ola, Mohd Imtiaz Nawaz,

ملخص مشروع رسالة ماجستير-٤

Ahmed Abu El-Asrar, Marwan Abouammoh, A. S. Alhomida (2013). Reduced level of brain derived neurotrophic factor (BDNF) in serum of diabetic retinopathy patients and in the retina of diabetic rats. *Cell Mol Neurobiol*. 2013 Apr;33(3):359-67

4. Mohd Imtiaz Nawaz, Marwan Abdulrahman Abouammoh, A. S. Alhomida, Mubarak Alfaran, M. Shamsul Ola (2013), Potential future drugs and their targets in the treatment of diabetic retinopathy, *Medical Science Monitor* 26;19:300-8.
5. M. Shamsul Ola, Nawaz MI, Khan HA, Alhomida A.S. (2013) Neurodegeneration and neuroprotection in diabetic retinopathy.*Int J Mol Sci*. 28;14(2):2559-72
6. M. Shamsul Ola, Mohammed M Ahmed, Hashish Hatem-Abuo, Salim Alrejaie, A. S. Alhomida (2013). Telmisartan ameliorates neurodegeneration in diabetic rat retina, *Neurochem Res*, DOI: 10.1007/s11064-013-1058-4
7. M. Shamsul Ola, Abdulaziz M. Aleisa, Salim S. Al-Rejaie, Hatem M. Abuohashish, Mihir Y. Parmar, A. S. Alhomida, Mohammed M. Ahmed (2014) Flavonoid, morin inhibits oxidative stress, inflammation and enhances neurotrophic support in the brain of streptozotocin-induced diabetic rats *Neurological Sciences*. DOI 10.1007/s10072-014-1628-5
8. M. Shamsul Ola (2014) Effect of hyperglycemia on insulin receptor signaling in the cultured retinal Muller cells (Manuscript submitted) Biochem Biophys Res Commun. 2014. DOI: 10.1016/j.bbrc.2014.01.052. [Epub ahead of print]
9. Abdulaziz M Aleisa, Salem S Al-Rejaie, Hatem M Abuohashish, Mohammed S Ola, Mihir Y Prmar and

ملخص مشروع رسالة ماجستير-٤

	Mohammed M Ahmed (2014) Pretreatment of Gymnema sylvestre revealed the protection against acetic acid-induced ulcerative colitis in rats. BMC Complementary and Alternative Medicine doi: 10.1186/1472-6882-14-49. 10. Mohammad Shamsul Ola and A. S. Alhomida (2014) Neurodegeneration in diabetic retina and its potential drug targets. Current Neuropharmacology 12; 4. 80-86.