iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 8 **Issue:** XI **Month of publication:** November 2020

DOI: https://doi.org/10.22214/ijraset.2020.32350

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.429
Volume 8 Issue XI Nov 2020- Available at www.ijraset.com

Therapeutic Potential of Streptozotocin and it's Correlation with Human and Animal Sciences: A Review

Vipin Khasa[1], Vipul Chaudhary[2], Pamela Singh[3], Chawla Shashi[4]
[1, 2, 3]*Department of Biotechnology, Deenbandhu Chhotu Ram University, Murthal, Sonipat -131006, (Haryana), India*
[4]*Department of Microbiology, Gargi College, New Delhi*

Abstract: ***Streptozotocin (STZ) is a broad-spectrum antibiotic, belonging to nitroso group, used mostly for induction of diabetes in laboratory animals. Induction of diabetes is mediated through glucose transporter (GLUT2) which helps entry of STZ in β cells of islets of Langerhans of pancreas, leading to cell death by ATP depletion and oxidative stress. Additional possible factors involving in cell death and apoptosis include alteration in cellular metabolism and impaired function of mitochondria. One of the limitations in use of STZ is genotoxicity along with other side effects. More frequent reports of Multi-Drug resistance (MDR) of microbes, have been available recently which have increased pressure on pharmaceutic industry to explore possibility of use of previously known agents with antibacterial properties. STZ is a potential candidate that needs further detailed research for its use as an antibiotic, along with use in treatment of pancreatic tumors. The present review has made an effort to know the properties of already known along with its limitation and possible future improvement. The significant contribution of STZ in experimental studies of drugs in laboratory animal particularly rodents has reconfirmed its importance in modern scientific studies.***

Keywords: Streptozotocin, Diabetes, Pancreatic tumor, antibiotic

I. INTRODUCTION

Modern world is full of economic opportunities and scientific advancement, with the knowledge gained in past. This has led to some of the common medical ailment in humans and animals like Diabetes and Carcinoma. These two are leading cause of mortality in man-kind and companion animals, in almost all the countries. Streptozotocin (STZ), which is antibiotic, originally derived from the bacterium *Streptomyces achromogenes* have also been used to destroy few types of cancinogenic growth (Lewis and Barbiers, 1959). STZ [N-(methylnitrosocarbamoyl)-α-D-glucosamine], a glycosourea family, drug is broad spectrum antibiotic, acting against both Gram-positive and Gram-Negative bacterium, is a DNA alkylating agent (Arwa *et al.*, 2017). Focus of this review is on existing knowledge of STZ, its antibiotic properties and its application in clinical management of cancer and understanding of non-communicable disease Diabetes, and studies on drugs used for diabetes treatment.

A. Streptozotocin (STZ)

An antibiotic initially identified in late 1950s from strains of *Streptomyces achromogenes*, as soil microbe, by scientist of Upjohn Company of Kalamazoo, Michigen, found effective against gram negative bacteria, later found to cause diabetes (Vavra *et al.*, 1959; Sithole *et al.*, 2009;Dyke at al., 2017.; Rakieten *et al.*, 1963). It is nitrosourea family alkylating agent, structurally similar to glucose resulting in competitive uptake by the glucose transporter 2 (GLUT2) protein but not taken by any other transporter, making it selectively toxic to β cells of islets of Langerhans of pancreas being richer in GLUT2 concentration (Northrup *et al.*, 2013 and Schnedl *et al.*, 1994). It is widely used in laboratory animal experiments for induction of diabetes and studying effect of various drugs like Quercetin, Thymoquinone (Atta *et al.*, 2018) and other physiological parameter like exercise (Camelia *et al.*, 2013). It has been approved for use in treatment of patients of cancer alone or in combination with other drugs of chemotherapeutic potential like Vincristin but genotoxicity and myelo-suppress remain most reported side effect (Bolzan *et al.*, 2002; Togni *et al.*, 1982; Clamon *et al.*, 1987). Use of STZ against *Staphycoccus aureus* has also been documented in vivo but no antibacterial activity found in-vitro (Yeo *et al.*, 2018).

B. Diabetes

One of the most commonly prevalent endocrine-metabolic ailments is Diabetes mellitus (DM), results due to genetic or environmental influences. Insulin metabolism disturbances leads to modify carbohydrates, lipids, and protein metabolisms [Yin *et al.*, 2014]. DM, is well known for high morbidity and mortality rate (Di Naso *et al.*, 2011), which is increasing due to more

sedentary lifestyle and urbanization (Camelia *et al*., 2013). Mycocardial variations have also been reported in DM which includes fibrosis, hypertrophy characterizing diabetic cardiomyopathy (Atta *et al*., 2018), leading to cardiac failure (Tziakas *et al*., 2005).

Insulin is secreted by β cells of islets of Langerhans in pancreas, which accounts for 60-70% islets proportion, while function of other islets cells β cells remain secretion of glucagon and δ cells secrete somatostatin polypetide hormone (Table 1).

Any increase in glucose concentration in extracellular fluid, stimulates release of insulin, which also increases under certain condition in response to other sugars, amino acids, hormones and drugs (theophylline, sulfonylurea). Insulin primarily stimulate carbohydrate, fats, protein and nucleic acid anabolic reactions. Three organs (Liver, muscle, adipose tissue) are primary targets sites for insulin, where it mainly increases glucose transport across membrane, along with decrease rate of lipolysis, proteolysis and gluconeogenesis. Maintenance of glucose level in extracellular fluid is performed by coordination of insulin and glucagon (The Mercks Veterinary Manual, 2016).

Pathogenesis of DM studies during last few decades, have been suggestive of oxidative stress implication (Camelia *et al*., 2013). Reactive oxygen species (ROS) formation occur due to increased creation of superoxide anions radicles, protein glycation and auto-oxidation of glucose (Formagio *et al*., 2013). Cell death and insulin resistance results because of ROS formation.

Table 1. Physiology of pancreatic cell types and their function

S. No.	Endocrine/ Exocrine	Pancreatic	Proportion	Function
1	Endocrine	α cells islets of Langerhans	Minor	Secretion of glucagon
2		β cells islets of Langerhans	Major (60-70%)	Secretion of insulin
3		δ cells islets of Langerhans	Minor	Secretion of somatostatin
	Exocrine	Acinar cells	Major	Digestive juice secretion

C. Diabetes Mallitus in Animals

Beside DM being a major endocrine metabolic disorder for human, other animals particularly middle aged dogs and middle aged to older cats also gets affected (The Mercks Veterinary Manual,2016). Among these, female dogs got affected twice the male counter-part (Table 2).

Table 2. Detail of prevalence of Diabetes Mallitus (DM) in animals other than human

S. No.	Species	Sex predilection	Age predilection	Breed predilection
1	Dog	Female	Middle aged	Miniature Poodles, Daschunds, Schnauzers, Cairns Terriers, Beagles
2	Cat	Male	Middle age to older	NA

D. Role of STZ in Diabetes

STZ injection in high doses develop type-1 diabetes whereas lower dose injection results in type-2 diabetes. High dose of STZ kills almost all β cells of pancreas whereas only few β cells got killed after administration of lower dose., leading to increased blood glucose levels (upto 500mg/dl) in injected rats in type-1 diabetes but reaches in diabetes type-2, comparative less elevation of blood glucose level (upto 300mg/dl) (Dyke *et al*., 2017). It has been reported that STZ has remain diabetogenic whether administered in fed or fasted mice (Chaudhry et al., 2013). It enters β cells through GLUT2, acts as nitric oxide (NO) donor leads to cell death (Fig.1). It increases O-linked protein phosphorylation in islets (Konrad *et al*., 2001). STZ contains DNA alkylating group, which leads to cytotoxicity on β cells, by poly-ADP-ribophosphorylation resulting in depletion of adenosine triphosphate (ATP) leading to oxidative stress (Arwa et al., 2017 and Yamamoto *et al*., 1981).

E. Use of STZ in Cancer Treatment

STZ has also been used in treatment of pancreatic cancer, insulinomas either alone or with vincristine, 5-fluorouracil, procarbazine or 6-thioguanine. It has also been used for treatment of gasterointestinal cancers but main underdesired side effect reported was toxicity and myelosuppression (Bolzan *et al*., 2002 and. Togni *et al*., 1982). Combination of STZ with doxorubicin use has also been recommended for pulmonary chemodectomas treatment (Chow *et al*., 1998).

F. Pancreatic tumor in Animals and use of STZ

Animals particularly canines have been detected with insulinomas which differ from Humans in that former develop malignant variant whereas later grow benign adenomas in majority of cases (Goural *et al*., 2012). All breed of dogs can be affected with insulinomas but more prevalent in larger breeds (Grant et al., 2016). Compared to human in which female develop more insulinomas, no difference was observed among different sex. Clinical signs include hypoglycemia, ataxia and collapse. Use of STZ (500mg/m^3 every 2 to 3 weeks) has been reported for treatment of insulinomas but wide varied degree of success. Adverse effect like human reported in canine includes vomiting, diarrhoea and increased alanine aminotransferase and DM. Reports shows neutropenia or thrombocytopenia was not observed in STZ administered dogs (Northrup *et al*., 2013).

G. STZ Antibiotic Potential

One of the current concern of medicos, veterinarian and public health professional is increasing prevalence and development of multi-drug resistance (MDR) in human, animals and food. Resistance to antibiotic got transferred and acquired by bacteria and fungi, through mechanism of mutation and horizontal transfer in environment (Kung *et al*., 2010., Miro-Canturri *et al*., 2019, Khasa *et al*., 2018). Development of new drugs is comparatively slower as suggested by World Health Organisation (WHO) (Tacconelli *et al*., 2018), which may lead to a "post antibiotic era'. Repurposing of existing drugs is now being explored to combat challenges posed by microbes (Rampioni *et al*., 2017 and Miro-Canturri *et al*., 2019). One of the most resistant bacteria in livestock and human is Gram-positive *Staphyloccus spp*., against which different drugs are being prepared along with possible use of previously existing less used antibiotic and other drugs including anthelmintic agents (Table 3) such as niclosamide and oxyclozanide (Rajamuthiah *et al*., 2015), ivermectin (Ashraf *et al*., 2018). STZ has also been found effective against *Staphyloccus* spp. in-vivo (Yeo at al., 2018) but other drugs like floxuridine has been found more useful in treatment in-vivo. The limitation of less activity, has been addressed in recent research on development of new drugs by modification at the C3 position of STZ to improve efficacy and to reduce toxicity (Zhang *et al*., 2020). Structural modification assay resulted in more inhibition of bacterial growth by Keto-STZ but was also found most cytotoxic. Another structural variant allo-STZ was found to carry moderate antibacterial activity and no cytotoxicity activity (Fig.2). These analogue generation is mediated by oxidation, inversion and reduction method. For the aim of repurposing STZ as antibiotic, recent studies showing its effectiveness in-vivo along with possibly improved STZ with improve activity and decreased toxicity, the future seems to be promising.

Table 3. Drugs having potential antibacterial activity against *Staphylococcus aureus* for re-purposing.

S. No.	Drug	Class of drug	Mechanism of action	References
1	Oxyclozinide	Anthelmintic	Damage of bacterial membrane	Imperi *et al*., 2018
2	Streptozotocin	Antibiotic, Anti-neoplastic	SaeRS complement system inhibition	Yeo *et al*., 2018
3	Floxuridine	Anti-neoplastic	SaeRS complement system inhibition	Yeo *et al*., 2018
4	Auranofin	Anti-rheumatic drug	Protein synthesis and inhibition of DNA synthesis	Thanugamani *et al*., 2016

H. STZ Usages in Experimental biology

Various drugs behave differently in-vivo and may be similar or different to in-vitro property. This has necessitated establishment of result by in-vivo assays in laboratory animals. For this purpose, rats and mice are preferred laboratory animals, which are off-fed for around a week's time before administration of STZ (40-50mg/kg b.wt.). As per recommendation of National Institute of Health (NIH) consortium, mice need to be fasted for 5-6 days prior to STZ administration (Chaudhry *et al*., 2013). This leads to development of diabetes in target rats and mice which when compared to control groups serve the basis for declaring any drug

safety before use for human and/or other members of animal kingdom. Most of countries follow well documented rules for use of laboratory animals for experimental studies. One of the most commonly used drugs for diabetes and cancer studies is STZ, which has improved our scientific knowledge based on evidence of in-vivo assays. Although well fed mice also develop diabetes after administration of STZ, which has been suggested to reduce stress hormones in laboratory animals (also for diabetes insipidus assays), it has been a practice to use off-fed mice till now (Chaudhry *et al*.,2013). Causes of diabetes and pathological manifestation could be successfully explored based on experiments on STZ induced rats/mice.

STZ generate a nitric oxide-oxygen based toxins, which suggested that STZ generate the peroxynitrite, a process in STZ-diabetes pathways (Dyke *et al*., 2017). Similarly, it has been demonstrated that thymoquinone (TQ) drug decreases plasma nitric oxide and increases total superoxide dismutase (T.SOD) activity in STZ treated diabetic rats. This suggested that oral intake of TQ prevents diabetes induced cardiomyopathy via inhibitory effect on cytokines and C-reactive proteins (Atta *et al*., 2018). Similarly, Quercetin, a flavonoid, having antioxidant property could prove its usages (Camelia *et al*., 2013) in diabetes by decreasing glucose level.

Further, experimental studies of many herbal drugs were made possible because of STZ induced diabetic animals. Many countries like China, Nepal, Egypt and India have traditional knowledge of herbal medicine and Ayurveda, but their scientific evidence might re-assure their claim. Indian Ayurveda mention that cow urine has antidiabetic properties. Distillate of cow urine after administration in STZ- treated diabetic mice, results in increased HDL levels and gain in body weight because of possible presence of antioxidants (Gururaja *et al*., 2011).

II. CONCLUSION

STZ, broad spectrum antibiotic, has been successfully used in treatment of cancer in human and animals, particularly for insulinomas and other gastrointestinal cancer. Although some genotoxicity has necessitated efforts for discovery of new anti-cancer agents with fewer toxicity. Certain modifications in STZ have evidence of reduction in genotoxicity along with better antimicrobial and anti-cancer efficacy. MDR has rendered most of the antibiotic un-useful particularly at safe therapeutic prescribed doses. The need for re-purposing older known antibiotics and other drugs like anthelmintics and anti-cancer drugs has once again shifted focus on lesser used STZ but limitation is that it has limited in-vitro activity along with possible DM. Pharmacological assays on laboratory animal needs diabetic host which is achieved by STZ injections. Further work on structural modification of STZ may increase its potential therapeutic use along with current purpose of induction of diabetes.

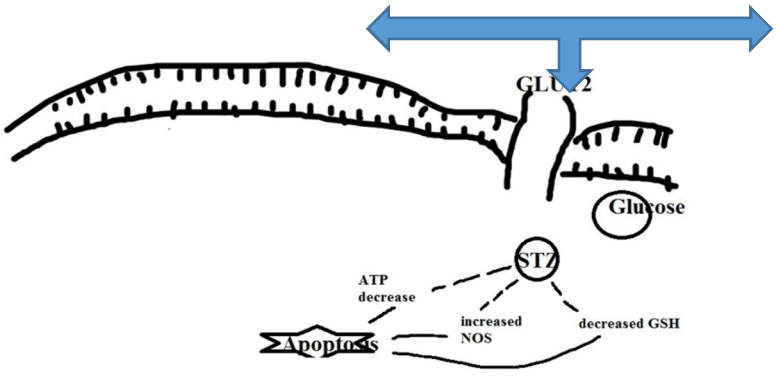


Fig. 1. Pictorial representation of STZ mediated cytotoxicity.

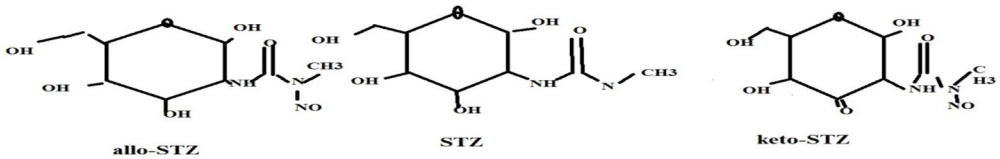
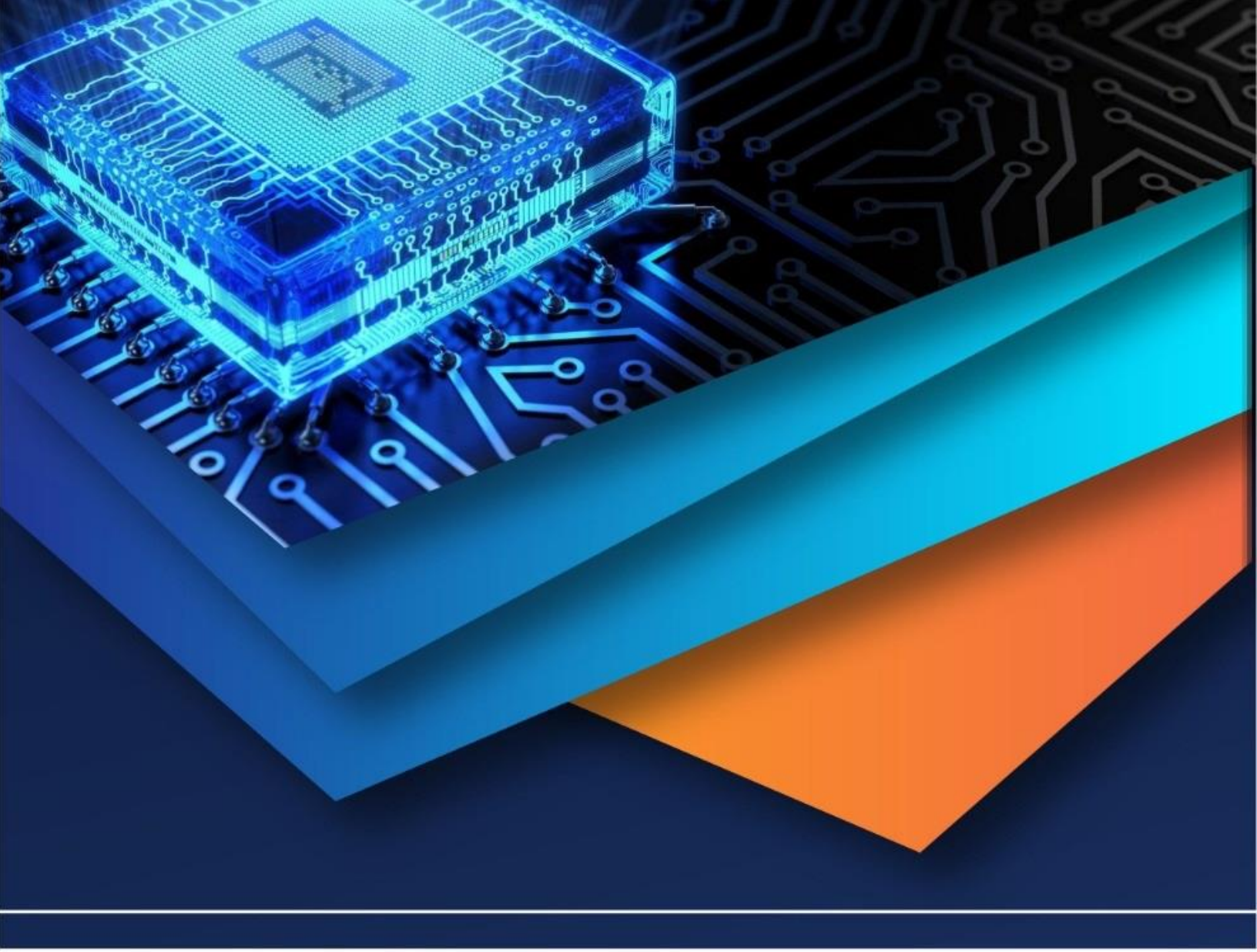


Fig. 2: Streptozotocin (STZ) structure and two allelic forms

REFERENCES

[1] Arwa M. T. Al Nahdi, Annie John, and Haider Raza. (2017). Elucidation of Molecular Mechanisms of Streptozotocin-Induced Oxidative Stress, Apoptosis, and Mitochondrial Dysfunction in Rin-5F Pancreatic β-cells. *Oxidative Medicine and Cellular Longevity*. Article ID 7054272, 15 pages https://doi.org/10.1155/2017/7054272.

[2] Ashraf, S., Chaudhry,U., Raza,A., Ghosh,D. and Zhao,X. (2018). In Vitro activity of ivermectin against Staphylococcus aureus clinical isolates. Antimicrobial Resistance and Infection Control. 7:27. Doi; 10.1186/s13756-018-0314-4.
[3] Atta , M.S., El-Far ,A.H., Farrag,F.A., Abdel-Daim ,M.M., Al Jaouni,S.K. and Mousa,S.A. (2018). Thymoquinone Attenuates Cardiomyopathy in Streptozotocin treated Diabetic Rats. Oxidative Medicine and Cellular longevity. Article ID 7845681, 10 pages. http;/doi.org/10.1155/2018/7845681.
[4] Bolzan,A.D, Bianchi,M.S. (2002). Genotoxicity of Streptozotocin. Mutation research. 512. 121-134.
[5] Camelia, C.R., BALTARU,D., MAIER, M., MURESAN,A. and CLICHICI,S. (2013). Effects of Quercetin and Chronic (Training) Exercise on Oxidative Stress Status in Animals with Streptozotocin-Induced Diabetes. Bulletein UASVM, Veterinary Medicine. 70(1).31-39.
[6] Chaudhry, Z.Z., Morris, D.L., Moss, D.R., Sims, E.K., Chiong,Y., Kono,T. and Evans-Molina, C. (2013). Streptozotocin is equally diabetogenic whether administered to fed or fasted mice. Laboratory Animals. 47(4); 257-265.
[7] Chow, S.N., Seear, M., Anderson, R. and Magee, F. (1998). Multiple pulmonary chemodectomas in a child: results of four different therapeutic regimens. Journal of Pediatric Hematology Oncology. 20.583–586.
[8] Clamon,G., Riggs,C., Stegink,L. and M. Traves. (1987). Phase 2 trial of Streptozotocin by continuous infusion for metastatic colorectal carcinoma, Cancer Drug Deliv. 4 43–46.
[9] Di Naso, F.C., Simoes Dias, A., Porawski, M., Marroni, N.A. (2011). Exogenous superoxide dismutase: action on liver oxidative stress in animals with streptozotocin-induced diabetes. Experimental Diabetes Research. Volume 2011 (2011), Article ID 754132, 6 page.
[10] Dyke,K.V., Geldenhuys, W. and Robert, A. (2017). Streptozotocin generates peroxynitrite luminescence which reveals the probable cause of diabestes 1,2 and 3 (Alzheimer's disease). International journal of Open access Opthalmology. Page 8. Open access.
[11] Formagio, A.S.N., Kassuya, C.A.L., Neto, F.F., Volobuff, C.R.F., Iriguchi, E.K.K., Vieira,M., Foglio, M.A. (2013). The flavonoid content and antiproliferative, hypoglycaemic, anti-inflammatory and free radical scavenging activities of Annona dioica St. Hill. BMC Complementary and Alternative Medicine. 13:14- 22.
[12] Goural, C.M., Brugmann, B.L. and Ryan. K.A. (2012). Insulinoma in dogs. A rieviw. JAAHA. 48:151-163.
[13] Grant, E.R. and Burgress, K.M. (2016). Canine Insulinoma: Diagnosis, Treatment and Staging. Today's Veterinary Practice. Pp. 60-64.
[14] Gururaja, M.P., Joshi, A.B., Joshi, A.B., Sathyanarayana, D., Subrahmanayam,E.V.S. and Chandrashekhar, K.S. (2011). Antidiabetic potential of cow urine in streptozotocin-induced diabetic rats. Asian Journal of Traditional Medicines. 6(1): 8-13.
[15] Khasa,V., Singh, P. and Sidhu,P.K. (2018). Plasmid profiling of Salmonella Typhimurium isolates from commercial poultry farms of Haryana. International journal of Pharmacy and Biological Sciences.8(4):154-159.
[16] Konrad, R.J., Mikolaenko,I., Tolar, J.F., Liu, K. and Kudlow, J.E. (2001). The potential mechanism of the diabetogenic action of streptozotocin: inhibition of pancreatic beta-cell OGlcNAc-selective N-acetyl-beta-D-glucosaminidase. Biochemical Journal . 356(Pt 1): 31–41.
[17] Kung, V.L., Ozea, E.A. and Hauser,A.S. (2010). The accessory genome of Pseudomonas aeruginosa. Microbiology and Molecular Biology Review. 74:621-641.doi:10.1128/mMBR.00027-10.
[18] Lewis,C. and Barbiers,A.R. (1959). "Streptozotocin, a new antibiotic. In vitro and in vivo evaluation," *Antibiotics Annual*, vol. 7, pp. 247–254.
[19] Miro-Canturri, A., Ayerbe-Algaba,R. and Smani,Y. (2019). Drug repurposing for the treatment of bacterial and fungal infections. Frontier in Microbiology. 10(41). 12 pages. Doi.10.3389/fmicb.2019.00041.
[20] Northrup, N.C., Rassnick, K.M. , Gieger, T.L., Kosarek, C.E., McFadden, C.W. and Rosenberg, M.P. (2013). Prospective Evaluation of Biweekly Streptozotocin in 19 Dogs with Insulinoma. Journal of Veterinary Internal Medicine. 27:483-490.
[21] Rajamuthiah, R., Fuchs, B.B., Conery, A.L., Kim.W., Jayamani, E., Kwon, B. et al. (2015). Repurposing salicylnilide anthelmintic drugs to combat drug resistant Staphycloccus aureus. PLos One. 10:e0124595.doi:10.1371/ journal. Prone.0124595.
[22] Rakieten, N., Rakieten, M. and Nadkarni, Mv. (1963). Studies on the Diabetic Action of Streptozotocin (NSC 37917). Cancer Chemotherapy Reports. 29:91-98.
[23] Rampioni, G., Visca, P., Leoni, L., and Imperi, F. (2017). Drug repurposing for antivirulence therapy against opportunistic bacterial pathogens. Emerging Topics in Life Science. 1, 13–23. doi: 10.1042/ETLS20160018.
[24] Schnedl, W.J., Ferber,S., Johanson, J.H. and Newgard,C.B. (1994). STZ transport and cytotoxicity. Specific enhancement in GLUT2-expressing cells. Diabetes. 43:1326-1333.
[25] Sithole, H.L. (2009). A review of the use of Streptozotocin (STZ) in the induction of diabetes in rats and subsequent ocular tissue changes. South African Optometrist. 68(2).82-88.
[26] Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., et al. (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infectious Disease. 18, 318–327. doi: 10.1016/S1473-3099(17)30753-3.
[27] The Mercks Veterinary Manual. 11th Edition. 2016. Merck and Co. Inc. Kenilworth, USA.pp.579-583.
[28] Togni, P., Sessa,C., Varini,M. and Cavilli,F. (1982). The combination of methyl-CCNU, vincristine, 5-fluorouracil and streptozotocin in the treatment of advanced colo-rectal adenocarcinoma, Schweizerische Medizinische Wochenschrift. 112. 930-933.
[29] Tziakas, D. N., Chalikias, G. K. and Kaski, J. C. (2005). "Epidemiology of the diabetic heart," Coronary Artery Disease, vol. 16, Supplement 1, pp. S3–S10.
[30] Vavra, J.J., Deboer, C., Dietz, A., Hanka, L.J. and Sokolski, W.T. (1959). Streptozotocin, a new antibacterial antibiotic. Antibiotic Annual. 7. 230–5.
[31] Yamamoto, H., Uchigata,Y. and Okamoto,H. (1981) "Streptozotocin and alloxan induce DNA strand breaks and poly(ADP-ribose) synthetase in pancreatic islets," Nature, vol. 294, pp. 284–286.
[32] Yeo,W.S., Arya,R., Kim,K.K., Jeong,H., Cho,K.H. and Bae, T. (2018)..The FDA-approved anti-cancer drugs, streptozotocin and floxuridine, reduce the virulence of Staphylococcus aureus. Scientific Reports. 8:2521.DOI:10.1038/s41598-018-20617-5.
[33] Yin,L., Cai, W. J. and Chang, X. Y. et al., "Association between fetuin-a levels with insulin resistance and carotid intimamedia thickness in patients with new-onset type 2 diabetes mellitus," Biomedical Reports, vol. 2, no. 6, pp. 839–842, 2014.
[34] Zhang,Ji., Yakovlieva, L., Haan,B.J., Minnaard, A.J., Witte, M.D. and Walvoort,T.C. (2020). Selective modification of Streptozotocin at the C3 position to improve its bioactivity as antibiotic and reduce its cytotoxicity towards insulin-producing β cells. Ntibiotics. 9. 182.doi.:10.3390/antibiotics9040182.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY