Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 10 [3] February 2021 : 36-41

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Synergistic anti-hyperglycemic activity of *Coriandrum sativum* with Metformin in Streptozotocin-induced Diabetic Rats

Uppuluri Spandana*[1,2], Adikay Sreedevi[2], Kaveripakam Sai Sruthi[2]
[1]Department of Pharmaceutical Chemistry, Nirmala College of Pharmacy, Atmakur, A.P, India.
[2] Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati, A.P, India.
Corresponding author e-mail: spuppuluri@gmail.com

ABSTRACT
Coriandrum sativum is a culinary herb whose seeds and leaves are used commonly in flavoring various food items. The seeds of this plant are associated with number of pharmacological benefits including anti diabetic potential. Worldwide diabetes is the most prevailing disease and many of the diabetic patients are regularly consuming oral hypoglycemic drugs like Metformin. So, there is a probability of herb drug interaction when the herb interferes with the way a drug acts in the body. Hence the present study is designed to explore the herb drug interactions of Coriandrum sativum powder with an oral hypoglycemic drug Metformin in Streptozotocin induced diabetic rats. In the present study animals were divided into seven groups of six each. Group-I served as normal control, Group-II and III received Metformin and aqueous extract of seeds of Coriandrum sativum. Diabetes was induced in animals of remaining groups using streptozotocin. Group IV served as diabetic control, Group V and Group VI treated with Metformin and Coraindrum respectively. Whereas Group-VII animals treated with both Metformin and seed extract. Pharmacokinetic interactions were studied after regular time intervals using HPLC –UV method. Further pharmacodynamic interactions were studied by estimating glucose levels and lipid profile on 1, 7, 14 and 21st day. Animals administrated with both Coraindrum sativum and Metformin showed significant potential in pharmacokinetic parameters by elevating the levels like Cmax, Tmax and Vd. Further pharmacodynamic studies showed synergistic antidiabetic effect in these animals by decreasing blood glucose levels and ameliorating the lipid profile when compared with Metformin and coriandrum alone treated diabetic rats. The findings of study evidences that there is a significant herb drug interaction occurred between Coriandrum sativum and Metformin. In conclusion, Coriandrum sativum can elevate the bioavailability of Metformin which seems to be beneficial in diabetic patients receiving Metformin.
KEYWORDS: *Coriandrum sativum, Metformin, anti diabetic, herb drug interaction.*

Received 02.01.2021 Revised 12.01.2021 Accepted 13.02.2021

INTRODUCTION

Culinary herbs have been grown and used for hundreds of years, and they are becoming increasingly popular for their knack to augment and complement the flavors of a wide diversity of foods [1]. *Coriandrum sativum* is one such culinary herb whose seeds and leaves are used commonly in flavoring various food items. In the Indian traditional medicine, a coriander is used in disorders of digestive, respiratory and urinary system, as it has diaphoretic, diuretic, carminative and stimulant [2]. Coriander has been reported to exhibit several pharmacological effects such as antioxidant activity, anticonvulsant activity, diuretic activity, cholesterol lowering activity, anticancer activity, hepatoprotective activity, antimicrobial activity and anti diabetic activity [3]. Pharmacological reports suggested that the seeds of *Coriandrum sativum* showed high therapeutic activity in reducing hyperglycemic in diabetes induced models [4].

Worldwide Diabetes mellitus is the most prevailing disease. It is an endocrine metabolic disorder characterized by hyperglycemia, altered lipids, carbohydrates, proteins, metabolism and it increases the risk of cardiovascular diseases complications [5]. The number of people with type 2 Diabetes mellitus is increasing in every country with 80% of people with suffering with this disorder living in low- and middle-income countries. Diabetes mellitus, caused by an absolute or relative deficiency of insulin or its function, lead to number of complications; it is emerging as the factor responsible for chronic disability and even death [6]. The disease has serious impact on health and quality of life in diabetic patients. Oral anti hyperglycemic agents are used generally to control diabetes. Metformin is one of the oral anti diabetic agents prescribed widely in diabetic patients and it exerts its pharmacological benefits by reducing hepatic glucose production and improving insulin sensitivity [7].

Co-administration of herbs either intentionally or unintentionally with Metformin like anti-diabetic drugs has reported increasing the need for evaluation of their possible interactions in diabetic conditions. Further more studies suggested that administration of Metformin with herbal products can be valuable in most of the cases [8]. A valuable synergistic effect can be additive blood sugar lowering effect but this effect can be harmful also when the sugar level goes down the normal level. Since there is a potential for the combined use of Metformin and *coriander* seeds by diabetic patients, present study is designed to explore the herb drug interactions of *Coriandrum sativum* powder with an oral hypoglycemic drug Metformin in Streptozotocin induced diabetic rats.

MATERIAL AND METHODS

Plant material: The *C. Sativum* seeds were obtained from Mangalagiri local market, and authenticated by the botanist of Acharya Nagarjuna University.

Preparation of extract: *C. Sativum* seeds were washed with water to remove dust, these seeds were shade dried after that powdered by using a mechanical grinder. The powder was subjected to aqueous extract by using the Soxhlet extraction method.

Phytochemical screening: The phytochemicals present in the aqueous extract of *C. Sativum* were screened using standard qualitative tests [9].

Animals:

Sprague Dawley (SD) rats were procured from Mahaveer enterprises, Hyderabad, India, these animals used for the studies after obtaining permission from the Institutional animal ethical committee (CPCSEA Reg. No018/IAEC/2017). The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light/dark cycle; at an ambient temperature of 25 ± 5 °C. The animals were fed with a standard rat pellet diet and water *ad libitum*.

Treatment protocol

Animals weighing 150 to 200g were divided into seven groups of six each. Group-I, II and III are normal animals and Group-IV, V, VI and VII are served as diabetic rats. Diabetes was induced in these groups by intraperitoneal injection of Streptozotocin (STZ) at a dose of 60mg/kg b.w. dissolved in 0.1 M citrate buffer, pH 4.5. Three days later, diabetes was confirmed by determination of fasting blood glucose levels in blood samples. Only rats with blood glucose level >250 mg/dL were considered diabetic and included in the study. The following treatment protocol was followed to study the herb drug interactions:

Group-I: Normal control
Group-II: Administered with Metformin (100mg/kg.b.w)
Group-III: Administered with Aqueous extract of seeds of *Coriandrum sativum* (400mg/kg.b.w)
Group-IV: Diabetic control
Group-V: Diabetic rats treated with Metformin (100mg/k.b. w)
Group-VI: Diabetic rats treated with *C.Sativum* high dose (400mg/k.b. w)
Group-VII: Diabetic rats treated with *C.Sativum* (400mg/k.b.w)+ Metformin (100mg/k.b.w)

Pharmacokinetic studies:

Pharmacokinetic studies were investigated in Group-V, VI and VII using the HPLC-UV system (cyber lab-Rx1600) analytical column C18 section (250x4.6mm id, 5µ). Blood Samples of selected groups were collected at predetermined time intervals of 0, 0.25, 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12, 24 hours (10 intervals). Plasma is immediately separated by centrifugation at 7500 rpm for 15 min. The concentration of drug in rat plasma samples is measured by the HPLC -UV method**.** The flow rate was kept constant at 1.5ml/min, the run time was 7 mins and the temperature was maintained at 500C. A mixer of Phosphate buffer- acetonitrile-methanol (40:40:20) was used as the mobile phase with UV detection at 368nm. All concentrations were calculated from a standard curve of Metformin obtained from spiked plasma samples. The Pharmacokinetic parameters like maximum plasma concentration (Cmax), time needed to reach the maximum plasma concentration (Tmax), area under the concentration– time curve (AUC0–24), mean residence time (MRT), elimination rate constant (Kel) and half life (T1/2) were determined.

Pharmacodynamic studies:

Pharmacodynamic studies were carried out by collecting the blood samples of animals at 1, 7,14, and 21st day and biochemical parameters namely blood glucose levels, TG, HDL, and VLDL were assessed using standard procedures. Further body weight is also monitored at the regular intervals [10].

Statistical analysis:

The values of pharmacokinetic and pharmacodynamic studies were expressed as mean ± SD. The data were statistically evaluated using a One-way analysis of variance (ANOVA). Values corresponding to the $p \leq 0.05$ were considered as significant.

RESULTS

Preliminary Phytochemical screening:

Preliminary phytochemical screening of aqueous extract of seeds of *C. sativum* revealed the presence of Alkaloids, Flavonoids, Tannins, Saponins, Carbohydrates, Proteins, Amino acids, Fatty acids and Terpenoids.

Pharmacokinetic studies:

The pharmacokinetic parameters were assessed in diabetic rats showed that co-administration of Metformin with *C. sativum* resulted in increase in peak plasma concentration (Figure 1). All the assessed pharmacokinetic parameters were mentioned in Table 1.

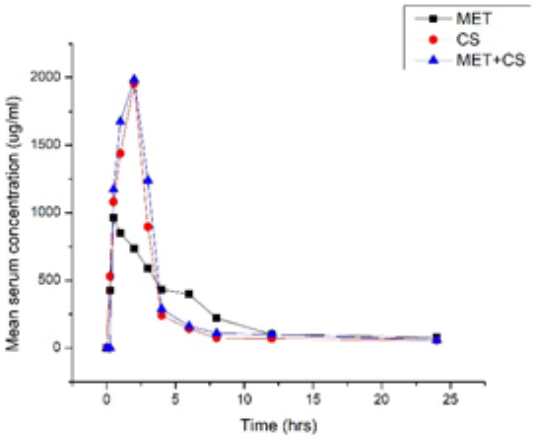

Figure 1: Mean serum concentration- time profiles of MET (Metformin), Coriandrum sativum (CS) and Co-administration of MET+ CS in diabetic rats

Table 1: Pharmacokinetic studies of Metformin with *Coriandrum sativum* in diabetic rats

Parameter	Metformin	*C. sativum*	Metformin with *C. sativum*
$C_{max(ng/ml)}$	987.33±0.45	1938.33±0.01	1974.00±.02
$T_{max\ (hl)}$	1.00±1.12	1.00±0.23	0.50 ±0.01
AUC $_{0\ to\ n(ng/ml*h)}$	4042.542±0.55	4077.881.02±1.10	5070.92±0.32
AUC $_{total\ (ng/ml*h)}$	0.943579±2.12	15280.004.50±0.12	66730.28±0.23
$t_{1/2(h)}$	5.73±0.55	2.36±1.12	2.88±0.51
MRT $_{(hl)}$	8.25±2.12	2.621±.02	3.37±0.63
$V_{d\ (ng/ml)}$	0.10±2.10	0.303609±0.45	0.37±0.35
Cl	0.01±0.06	0.008±0.96	0.09±0.45

Pharmacodynamic studies:

The effect of *C. sativum* and Metformin alone and in combination on various biochemical parameters on day 1, 7, 14 and 21 were assessed. The results showed that body weight was decreased in diabetic control animals significantly and upon administration of Metformin and extract there was significant increase in body weight. Moreover, the blood glucose levels which plays as an important parameter in diabetes were estimated and the results depicted that in diabetic animals upon inducing of Streptozotocin there was elevation in blood glucose levels and co-administration of metformin and *Coriandrum sativum* in combination declined the levels of blood glucose significantly compared with their individual treatment. In case of estimation of HDL levels, it was observed that in diabetic control animals HDL levels were declined and there was a significant shoot up in HDL levels in treated animals. Further the results revealed that co-administration of drug and extract in diabetic animals significantly decreased levels of triglycerides and VLDL (Figure 2).

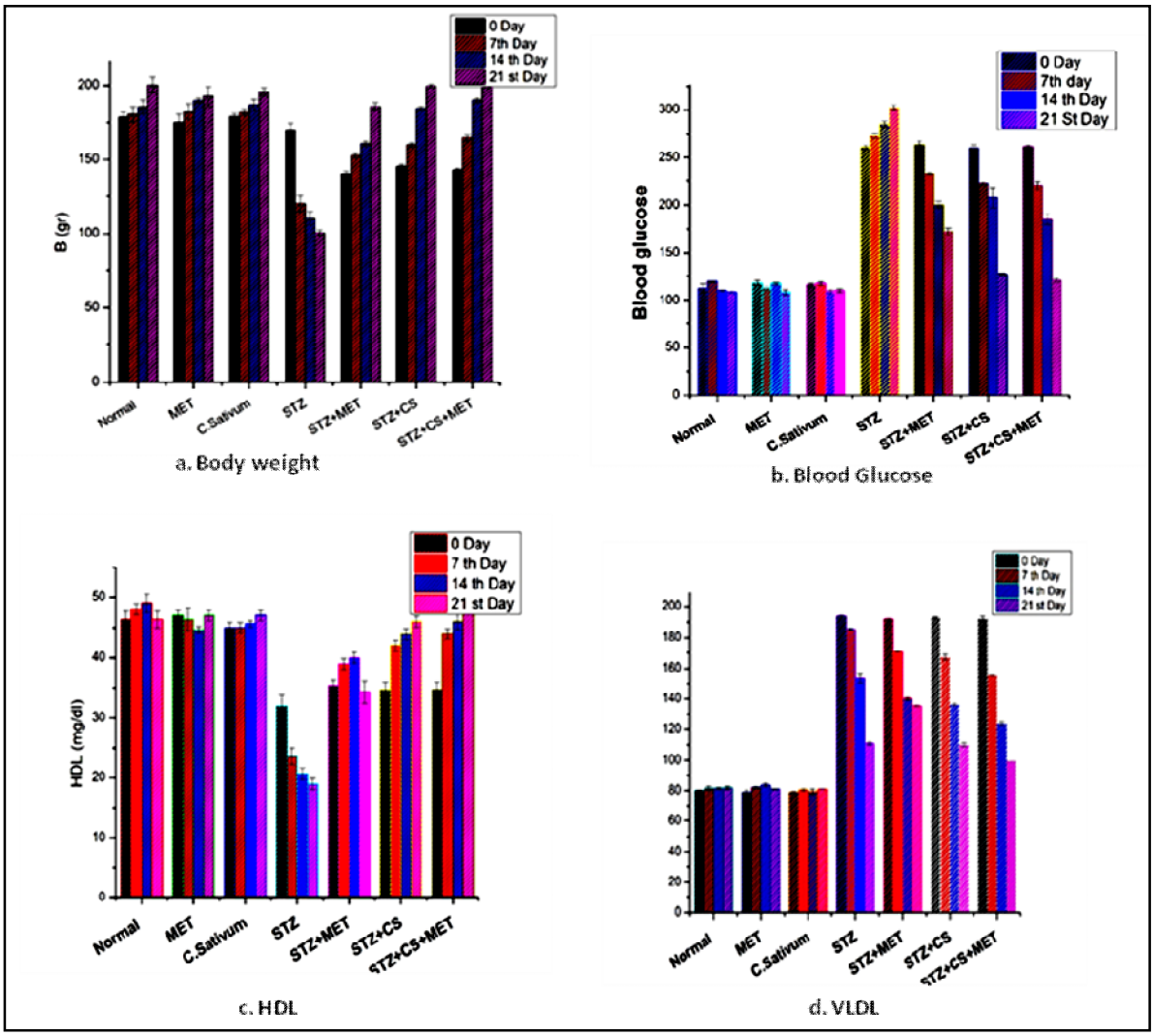

Figure 2: Pharmacodynamic studies of Metformin with *Coriandrum sativum* in normal and diabetic rats

DISCUSSION

Worldwide Diabetes is one of the most prevailing disorders in human kind. With increase in knowledge on heterogenicity of the disorder there is a raise in need for novel therapies. Certain allopathic drugs like Glibenclamide, Tolbutamide, Glipizide, Metformin are being used as first line drugs for treating this disorder [11]. Concurrently the use of herbal remedies also gained much importance. Among many herbal remedies *Coriandrum sativum* seeds are one of the promising remedies practiced by many people in world [12]. Such simultaneous use of herb and drug can interact with each other and may lead to herb drug interaction. Hence the current study lies in identifying the possibilities of potential interactions of seeds of *Coriandrum sativum* with the selected conventional drug i.e., Metformin.

In the present study pharmacokinetic and pharmacodynamic studies were performed to observe the interactions between the aqueous extract of seeds of *Coriandrum* and Metformin. Seed extract and Metformin are given alone and in combination in both normal and diabetic rats. Streptozotocin was used to induce diabetes in rats. The streptozotocin impairs glucose oxidation and leads to reduction in insulin biosynthesis and secretion. Further streptozotocin involves DNA alkylation induced generation of reactive oxygen species and increased formation of Nitric oxide in β cell of Pancreas [13, 14].

Pharmacokinetic study involves the quantification of standard drugs in the biological systems. In present study bioanalytical method using HPLC-UV was developed and the plasma levels of drug and extract was determined. The observations of our study demonstrated the role of Coriandrum in pharmacokinetics of Metformin. Absorption half life of Metformin when compared with co-administered group has declined by half indicating the interactions influence the delay of absorption, hence the drug is made available for longer period of time. These studies come in harmony with the earlier studies of pharmacokinetic herb drug interactions [15,16].

Further pharmacodynamic studies revealed that in consistent with previous reports in current study also biochemical parameters like body weight, blood glucose levels, Triglycerides, HDL and VLDL levels were altered significantly in diabetes induced animals [17,18]. This may be due to the impairment of insulin action in the conversion of glucose into glycogen and catabolism of fats and inhibition of lipolysis. However, treatment with Metformin and seed extract ameliorated significantly the altered levels due to induction of Diabetes. It is clearly noticeable from present observations that the combination of Metformin and *coriander* seeds effectively attenuated hyperglycemic conditions. This effect may be due to the beneficial effect of seeds of *Coriander* seeds in regeneration of pancreatic β cells which is clearly evident from the earlier reports [19].

Previous studies reported that many anti-diabetic drugs produce hypoglycemic action by potentiating the insulin effect either by increasing the pancreatic secretion of insulin from the β -cells or its release from bound insulin, whereas others may act *via* extra-pancreatic mechanism by inhibition of hepatic glucose production [20]. Seeds of *Coriandrum sativum* may also acted through any one of the mechanisms and it might contribute to the synergistic action of Metformin. Furthermore, earlier evidences showed that flavonoids and terpenoids have potent antioxidant activity which helps in the regeneration pancreatic cells and increase in insulin secretion in hyperglycemic patients [21, 22]. In our preliminary phytochemical studies, it was clear that the aqueous extract of Seeds of *Coriandrum sativum* was rich in bioactive phytoconstituents like flavonoids and terpenoids which might be responsible for increased anti hyperglycemic activity. Hence the simultaneous administration of seed extract of coriander and Metformin resulted in potential anti-hyperglycemic effect and this might be due to the interaction of bioactive phytoconstituents present in *coriander* seed extract with Metformin in the body.

CONCLUSION

The finding of study evidences that there was additive pharmacological potential with the combination of *Coriandrum sativum* and Metformin. Therefore, the seeds of *Coriandrum sativum* are valuable in therapeutic application for diabetes and it is conspicuous that there will be synergistic anti hyperglycemic effect when administered with Metformin. In conclusion, *Coriandrum sativum* can elevate the bioavailability of Metformin and thus due to the synergistic antihyperglycemic activity of *Coriandrum sativum* with Metformin the dose level of Metformin can be reduced to produce the equal therapeutic effect when administered alone.

CONFLICTS OF INTEREST

No Conflicts of Interest

REFERENCES

1. Nadeem, M., Anjum, F., & Khan, M. T., (2013). Nutritional and medicinal aspects of coriander (*Coriandrum sativum L.*) A review. British Food Journal.; 115.
2. Mahendra, P., (2011). *Coriandrum sativum*: A Daily Use Spice with Great Medicinal Effect. Pharmacogn J.; 3: 84–88.
3. Iqbal, M.J., Butt, M.S., Suleria, H.A. (2019). Coriander (*Coriandrum sativum* L.): Bioactive Molecules and Health Effects. In: Mérillon JM., Ramawat K. (eds) Bioactive Molecules in Food. Reference Series in Phytochemistry.; 1-37.
4. Das, S.C., Sanjeevani, N., Nimish, T., & Abhijeet, R., (2019). Antidiabetic activity of Coriandrum sativum in streptozotocin induced diabetic rats. Int J Basic Clin Pharmacol.; 8; 925.
5. American Diabetes Association., (2009) Diagnosis and classification of diabetes mellitus. *Diabetes Care.*; 32 Suppl 1(Suppl 1): S62-S67.
6. Chawla, A., Chawla, R., Jaggi, S. (2016) Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab*. 2016; 20(4):546-551.
7. Dumitrescu, R., Mehedintu, C., Briceag, I. (2015) Metformin-clinical pharmacology in PCOs. *J Med Life.*; 8(2):187-192.
8. Gupta, R.C., Chang, D., Nammi, S., Bensoussan, A., Roufogalis BD. (2017) Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications. *Diabetol Metab Syndr*. ; 9:59.
9. Shaikh, Junaid P, Matsyagandha. (2020). Qualitative tests for preliminary phytochemical screening: An overview. Int J Chem Sci.; 8: 603-608.
10. Choudhari, V.P., Gore, K.P., Pawar, A.T. (2017) Antidiabetic, antihyperlipidemic activities and herb-drug interaction of a polyherbal formulation in streptozotocin induced diabetic rats. *J Ayurveda Integr Med.*; 8(4):218-225.
11. Sola, D., Rossi, L., Schianca, G.P., et al. (2015) Sulfonylureas and their use in clinical practice. *Arch Med Sci.*; 11(4):840-848.
12. Maroufi, K., Farahani, H.A. & Darvishi, H.H. (2010). Importance of coriander (Coriandrum sativum L.) between the medicinal and aromatic plants. Adv Environ Biol.; 4: 433-436.

13. Eleazu, C.O., Eleazu, K.C., Chukwuma, S., Essien, U.N. (2013) Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *J Diabetes Metab Disord*.; 12(1):60.
14. Szkudelski T. (2001) The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. Physiol Res.; 50(6):537-46.
15. Gupta, R.C., Chang, D., Nammi, S., et al. (2017). Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications. *Diabetol Metab Syndr*.; 9:59.
16. Han, D.G., Cho, S.S., Kwak, J.H. *et al.* (2019). Medicinal plants and phytochemicals for diabetes mellitus: pharmacokinetic characteristics and herb-drug interactions. *J. Pharm. Investig.;* 49: 603–612.
17. Sushant, S., Kalyan, K., Dada, P., Sanjay, M., et al. (2018). Herb drug interaction of Nisha Amalaki and curcuminoids with metformin in normal and diabetic condition: A disease system approach. Biomedicine and pharmacotherapy; 101: 591-598.
18. Elango, H., Ponnusankar, S., Sundaram, S. (2015). Assessment of pharmacodynamic and pharmacokinetic interaction of aqueous extract of *Cassia auriculata* L. and metformin in rats, Pharmacog Mag.; 11(44): 423-426.
19. Eidi, M., Eidi, A., et al. (2009). Effect of Coriander Seed (Coriandrum sativum L.) Ethanol Extract on Insulin Release from Pancreatic Beta Cells in Streptozotocin-induced Diabetic Rats. Phytotherapy research: PTR.; 23: 404-6.
20. Amal, Z., Barakat, R. I., Bassuiny, Azza M. Abdel-Aty, Saleh A. Mohamed. (2020). Diabetic complications and oxidative stress: The role of phenolic-rich extracts of saw palmetto and date palm seeds. *J. Food Biochem.;* 44:11. 21. Choudhury, H., Pandey, M., Hua, C.K., et al. (2017). An update on natural compounds in the remedy of diabetes mellitus: A systematic review. J Tradit Complement Med.; 8(3):361-376.
21. Patel, D.K., Prasad, S.K., Kumar, R., Hemalatha, S. (2012). An overview on antidiabetic medicinal plants having insulin mimetic property. *Asian Pac J Trop Biomed*.; 2(4):320-330.

CITATION OF THIS ARTICLE

U Spandana, A Sreedevi, K S Sruthi. Synergistic anti-hyperglycemic activity of *Coriandrum sativum* with Metformin in Streptozotocin-induced Diabetic Rats. Bull. Env.Pharmacol. Life Sci., Vol10[3] February 2021 : 36-41