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In-Vitro Antioxidant Activity and Free Radical Scavenging Potential of Phlorizin Derived Sodium Glucose Cotransporter 2 Inhibitor

De A[1]*, Chattopadhyay P[2], Singh M[3]

[1] Department of Pharmaceutical Science, Bengal School of Technology, Hooghly, West Bengal, India

[2] Department of Biotechnology, National Institute of Pharmaceutical Education and Research (NIPER), Guwahati, India

[3] Department of Pharmaceutical Biotechnology Dr. Hari Singh Gour Vishwavidyalaya, Sagar, Madhya Pradesh, India

ABSTRACT

Objectives- *In vitro* antioxidant activity assay is the preliminary step to determine a drug's efficacy in combating oxidative stress when used in a clinical condition. The current study was aimed to determine the *in vitro* antioxidant activity of antidiabetic drug-SGLT-2 inhibitor (canagliflozin, dapagliflozin and empagliflozin) in combating the oxidative stress in diabetes mellitus. **Methods-** A total of five methods were adopted for determining the antioxidant potential of the drugs. The methods were DPPH radical scavenging assay, nitric oxide radical scavenging assay, phosphomolybdenum assay, assessment of inhibition of lipid peroxidation and FRAP. **Results-** The results indicated canagliflozin as best DPPH radical scavenger and empagliflozin as the best scavenger of nitric oxide radicals. Also, empagliflozin showed best reducing power and canagliflozin showed promising results in inhibiting lipid peroxidation. **Conclusion-** These findings suggest that use of canagliflozin and empagliflozin in diabetic patient will control the hyperglycemic conditions well as other complications that are caused by hyperglycemia induced oxidative stress.

Keywords- DPPH radicals, Lipid peroxidation, Oxidative stress, Phosphomolybdenum assay, SGLT-2 inhibitor

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***Address for Correspondence:**

Abhijit De, Assistant Professor, Department of Pharmaceutical Science, Bengal School of Technology, Hooghly, West Bengal,

INTRODUCTION

Canagliflozin, dapagliflozin and empagliflozin are the three phlorizin derived drugs recently approved for the treatment of type 2 diabetes mellitus. These drugs selectively inhibit SGLT-2 in kidney without affecting the intestinal SGLT-1. SGLT-2, the main reabsorption transporter of glucose in nephron, if inhibited, is likely to cause an increase in urinary glucose excretion in individuals with type 2 diabetes mellitus. The lower plasma glucose and greater urinary glucose excretion leads to a net loss of calories and weight loss and also the increased glucose in urine produce a mild osmotic diuresis that may contribute to reduction in systolic blood pressure. As urinary glucose excretion is dependent on glomerular filtration rate, the gliflozin analogues is likely to be less effective in patients with impaired renal function. As these drugs increase the urinary glucose excretion, they often produce adverse effects like genital mycotic infection or urinary tract infection and some other adverse effects associated with osmotic diuresis.

Our antioxidant defence system eliminates the reactive species (free radicals) and oxidative stress that occurs due to imbalance between production of free radicals and the reduced efficiency of antioxidant defence system against oxidants[1]. Amongst the various cause of diabetic complications, hyperglycaemia induced oxidative stress plays a key role[2]. Two main type of oxidants viz. reactive oxygen species includes free radicals like hydroxyl radicals (•OH), superoxide radicals (O_2• -) & non-free radicals like peroxides and reactive nitrogen species includes free radicals like nitric oxide (•NO), nitrogen dioxide (NO_2•-) & non-free radicals like peroxynitrite (OONO-)[3] cause other complications like Parkinson's disease[4], Alzheimer's Disease[5], COPD[6] and others that don't have direct connections with diabetes.

In type 2 diabetes mellitus, increased oxidative modification of plasma lipoprotein leads to increased peroxide lipid and lysophosphatidylcholine[7] and the peroxide lipid is accumulated in cardiovascular tissue causing macrovascular damage[8]. Diminished expression of nitric oxide synthase and

generation of NO_2, impaired expression of SOD, reduced level of antioxidant glutathione, α-tocopherol, ascorbate, hyperactivity of sorbitol pathway, enhanced protein glycosylation and AGE formation works all together in vascular endothelium to increase oxidative stress. Normal vascular endothelial functions are altered as a result and this is one of the pathogenic factor of vascular complications in several disease states including diabetes mellitus.

The current study was focused on investigation of combating the oxidative stress or free radicals by canagliflozin, dapagliflozin and empagliflozin. The assessment of in vitro antioxidant activity was done in five methods. The methods employed were DPPH radical scavenging assay, nitric oxide radical scavenging assay, FRAP, phosphomolybdenum assay and assessment of inhibition of lipid peroxidation.

MATERIALS AND METHODS

Chemicals

All the chemicals used were analytical grade. 2,2-diphenyl-1-picrylhydrazyl (DPPH) was purchased from Himedia laboratories, Mumbai, India. L-ascorbic acid, methanol, sulphanilamide, N-(1-naphthyl)-ethyl-enediamine dihydrochloride, orthophosphoric acid, sodium, ethanol, hydrochloric acid, potassium ferrocyanide, ferric chloride, sodium dodecyl sulfate, ammonium molybdate, disodium hydrogen phosphate dihydrate, sulphuric acid, ferrous sulfate heptahydrate, glacial acetic acid, trichloroacetic acid, thiobarbituric acid and butan-1-ol were purchased from Merck, Mumbai, India.

Determination of DPPH Radical Scavenging Assay

The DPPH scavenging assay was performed for all the three drugs at concentration 50-800µg/ml against reference compound ascorbic acid by previously described method[9] with some modifications. The drugs were solubilized in suitable solvents with vortexing for five minutes or until complete solubilization. 50µL of the drug solutions of each concentration were taken in a test tube followed by addition of methanol up to 3 ml. 150µL of 0.13% w/v solution of DPPH in methanol was then added in each test tubes and sufficient time was provided for the antioxidant action to take place. The absorbance of the solution was measured with UV-visible spectrophotometer (Schimadzu UV-1800) at 517 nm. The decrease in absorbance upon increasing drug concentration implicates more scavenging of free radicals. The % inhibition was calculated from the formula-

$$\% \text{ inhibition} = \frac{Abs\ of\ control - Abs\ of\ test}{Abs\ of\ Control} \times 100$$

Determination of Nitric Oxide (NO) Scavenging Assay

The method of Kang et al.,[10] was followed for the determination of nitric oxide radical scavenging potential. 5mM Sodium Nitropruside (SNP) in phosphate buffer saline pH 7.4 was used to generate NO which intermingles with oxygen to generate nitrite ions. Scavenging of the nitrite ions was assessed with Griess reagent (1% w/v sulphanilamide, 5% w/v phosphoric acid, 0.1% w/v N-(1-naphthyl)-ethyl-enediamine dihydrochloride). 1ml of sodium nitropruside was added to each drug concentration ranging from 50-800µg/ml followed by incubation at 25° C at light for 60 minutes and addition of equal volume of Griess reagent and incubation at same temperature at dark condition for 30 minutes. The diazotization of nitrite ions with sulphanilamide and subsequent coupling reaction with N-(1-naphthyl)-ethyl-enediamine dihydrochloride generates a pink chromophore, absorbance of which was measured at 546 nm. The % inhibition was calculated using the same formula as used in DPPH radical scavenging assay process

Ferric Ion Reduction by FRAP

The method of Prieto et al[11] was followed with some modifications. The principle behind this test is the ability of antioxidant to reduce Fe^{3+} to Fe^{2+} by electron donation. To the test tubes containing 100 µl drug solution with concentration ranging from 50-800 µl, 3 ml deionized water were added along with 90 µl of 95% ethanol. In the next step, addition of each of 150 µl of 1M HCl and 1% w/v potassium ferrocyanide was followed by addition of 50 µl of 1% sodium dodecyl sulfate. Finally, 20 µl of 0.2% ferric chloride was added which imparts Prussian blue color. For proper distribution of color, all test tubes were vortexed for 15 minutes. The absorbance was measured using UV-visible spectrophotometer (Schimadzu UV 1800) at 700 nm. The antioxidant activity of the drugs was evaluated taking ascorbic acid as standard.

Phosphomolybdenum Assay

The method of Prieto et al[11] was followed with some modifications. The principle of phosphomolybdenum assay is the reduction of phosphate-Mo (VI) to phosphate-Mo (V) by antioxidants. Tubes containing 100 µL drug solution of varying concentration (50, 100, 200, 400 and 800 µg/ml) were mixed with 1 ml deionized water and 1 ml of phosphomolybdenum reagent. Test tubes were labeled and heated at 95° C for 10 minutes. After cooling to room temperature, absorbances was taken at 695 nm. Antioxidant capacity was evaluated against standard antioxidant ascorbic acid.

Assessment of Inhibition of Lipid Peroxidation

Thiobarbituric Acid Reactive Substances (TBARS) method as described by Roberto et al[12] was adopted with slight modification for the assessment of extent of inhibition of lipid peroxidation using egg yolk homogenate as lipid rich media. 500 µl of 10% egg yolk homogenate was added to tubes containing 100 µl of drug solution of concentration ranging from 50-800 µg/ml. The volume of the tubes was made 1 ml with deionized water. 50 µl of 0.07M ferrous sulfate was added to all the tubes and incubated for 20 minutes to induce lipid oxidation. Then 1.5 ml of each of 20% acetic acid and 0.8% w/v thiobarbituric acid prepared in 1.1% sodium dodecyl sulfate were added to all tubes followed by addition of 50 µl of 20% w/v trichloroacetic acid. Tubes were then vortexed and heated for 1 hour at 95° C. After cooling to room temperature, 5 ml of n-butanol was added to each test tubes and centrifuged at 5000 rpm for 5 minutes. The organic upper layer was collected and absorbance was measured of each sample at 532 nm. The antioxidant capacity of the drugs was calculated as % inhibition taking ascorbic acid as standard.

RESULT

Determination of DPPH Radical Scavenging Assay

A dose dependent DPPH radical scavenging activity was shown by ascorbic acid (figure-1) and all the gliflozin analogues. At 800 µg/ml concentration, extent of DPPH radicals scavenging by ascorbic acid, canagliflozin, dapagliflozin, empagliflozin (figure-2), was 97.87%, 87.18±0.080%, 94.47±0.010% and 60.83±0.030%, respectively. The IC_{50} value shown by these drugs were 117.4 ± 0.02, 103.6 ± 0.06, 130.1 ± 0.06 and 294.1 ± 0.04 respectively for ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (Table 4).

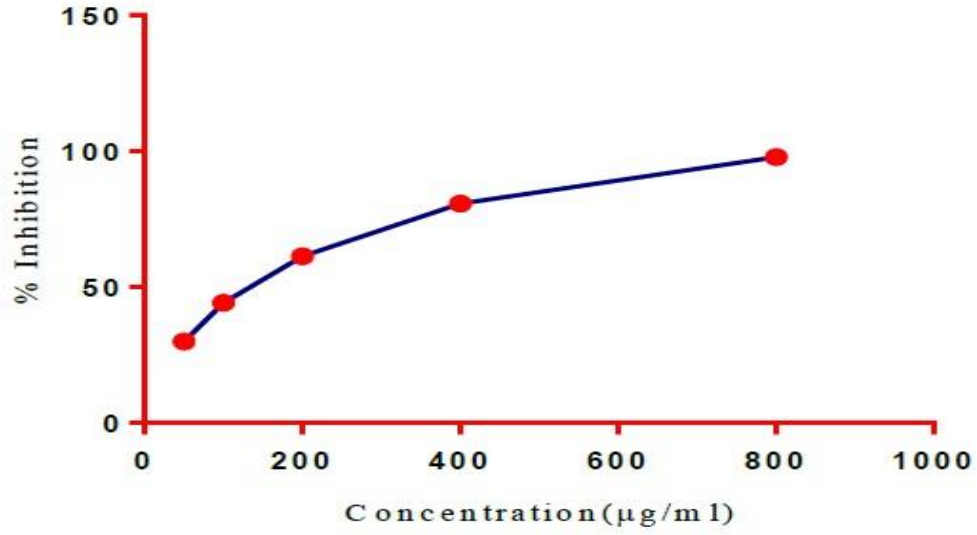

Figure 1: Standard curve of ascorbic acid in DPPH assay

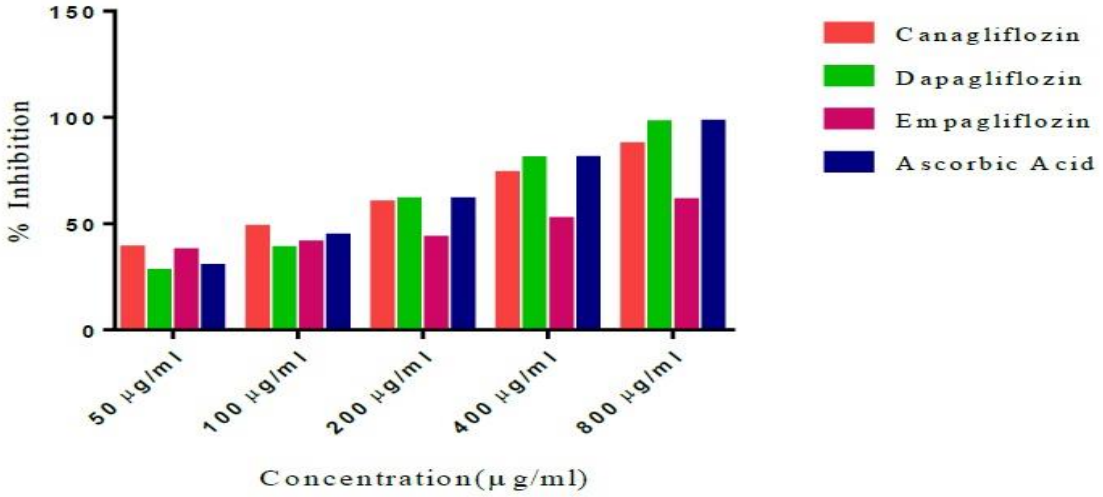

Figure 2: Antioxidant Potential of Gliflozin Analogues in DPPH assay

Nitric Oxide Scavenging Method

A dose dependent nitric oxide radical scavenging activity was established taking ascorbic acid as antioxidant (figure-3). All the gliflozin also followed more or less similar pattern. At 800 µg/ml, the extent of NO radical scavenging by ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (figure-4) was 87.16%, 66.77±0.140%, 68.23±0.080% and 72.80±0.115% respectively. The IC_{50} data of ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (table 4) were 93.64 ± 0.115, 331.5 ± 0.16, 210.9 ± 0.19 and 92.71 ± 0.06.

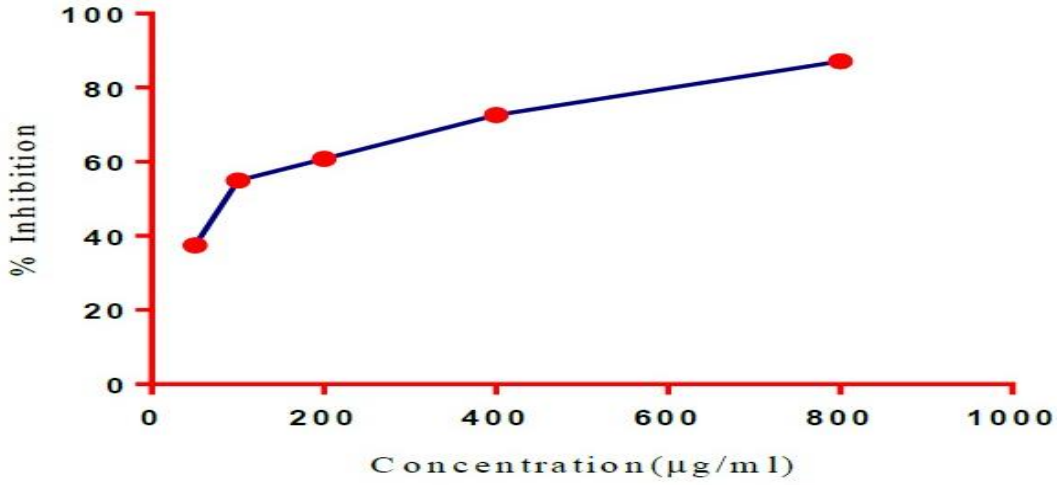

Figure 3: Standard curve of ascorbic acid in nitric oxide scavenging assay

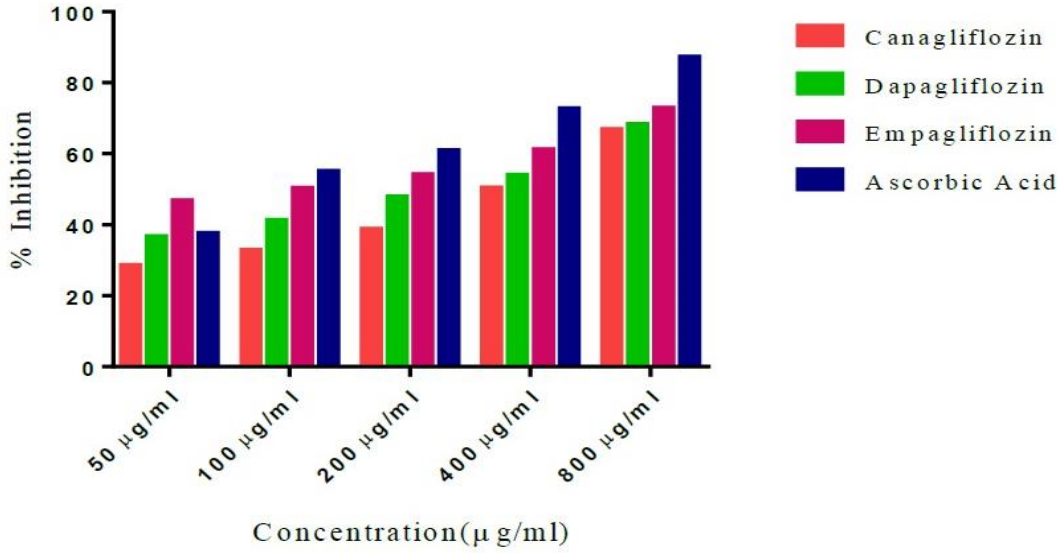

Figure 4: Antioxidant Potential of Gliflozin Analogues in NO scavenging assay

Ferric Ion Reduction by FRAP

The dose dependent increase in radical scavenging activity of ascorbic acid measured by FRAP process is shown in figure-5. All the drugs followed similar dose dependent radical scavenging activity. At 800 µg/ml, the % RSA of ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (figure-6) was found to be 98.47%, 74.18±0.080, 90.22±0.105 and 94.70±0.085 respectively. The IC_{50} data shown by these drugs and ascorbic acid were 271.2 ± 0.06, 350.6 ±0.09, 281.1 ±0.07, 264.1 ±0.16 (Table-4).

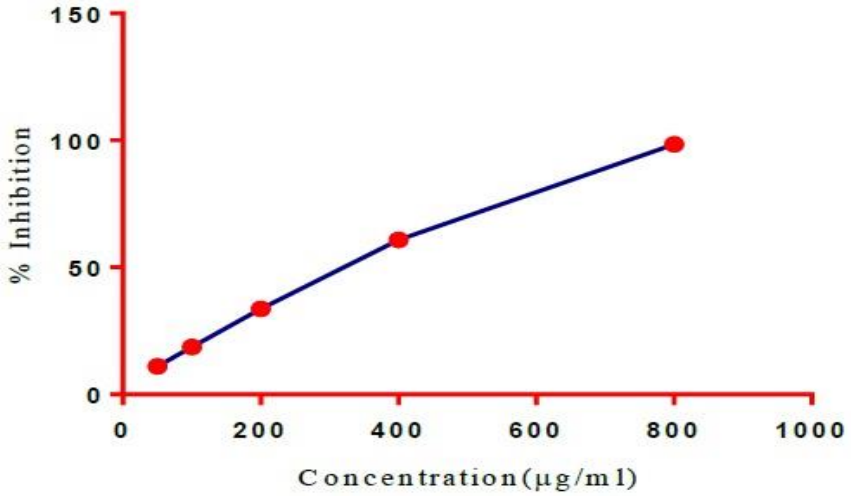

Figure 5: Standard curve of ascorbic acid in ferric ion reduction by FRAP

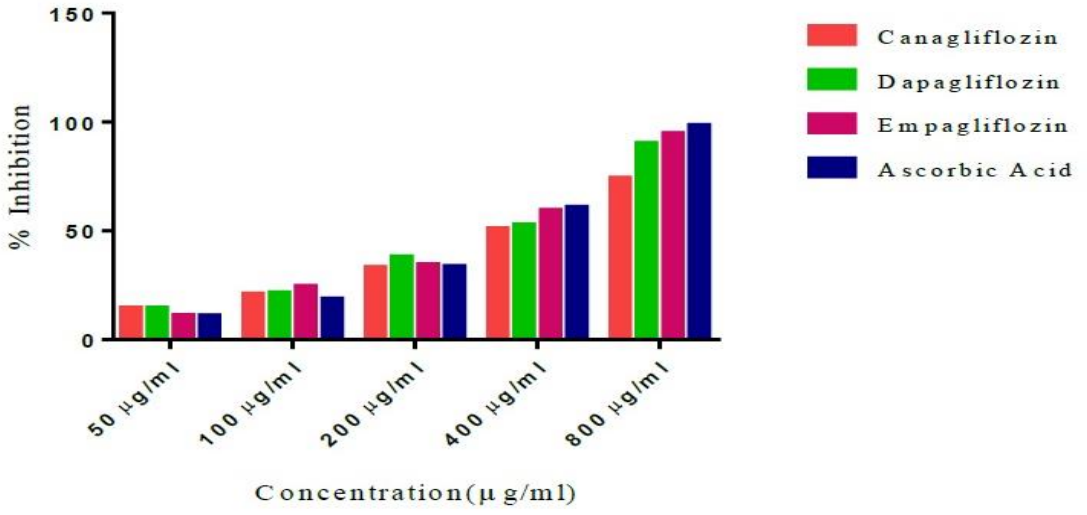

Figure 6: Antioxidant Potential of Gliflozin Analogues in ferric ion reduction by FRAP

Phosphomolybdenum Assay

A dose dependent increase in antioxidant activity of ascorbic acid was found when the extent of antioxidant activity was measured by phosphomolybdenum assay process (figure-7). The similar pattern of antioxidant activity was observed for all drugs. At 800 µg/ml concentration, the extent of antioxidant activity shown by ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (figure-8) was 99.36%, 98.63±0.045, 98.07±0.110 and 99.30±0.085. Table 4 contains IC_{50} values of all gliflozin analogues. The values were 174.3 ±0.04, 241.4 ±0.04, 344 ±0.11 and 272.3 ±0.07.

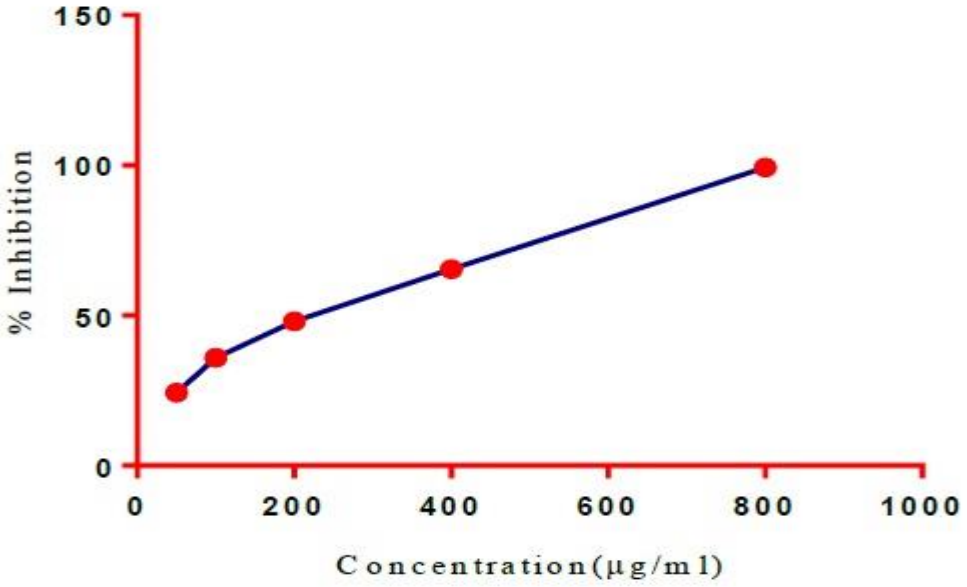

Figure 7: Standard curve of ascorbic acid in phosphomolybdenum assay

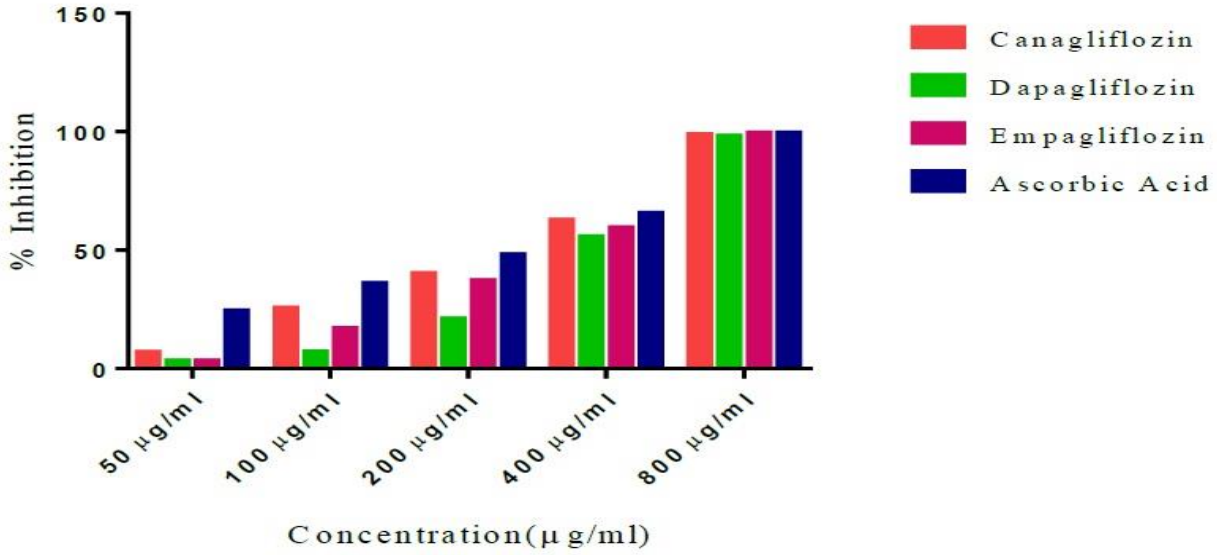

Figure 8: Antioxidant Potential of Gliflozin Analogues in phosphomolybdenum assay

Assessment of Inhibition of Lipid Peroxidation

The dose dependent increase in antioxidant power of ascorbic acid was established in the assessment of inhibition of lipid peroxidation (figure-9). The potential to inhibit the lipid peroxidation by ascorbic acid, canagliflozin, dapagliflozin and empagliflozin (figure-10), at concentration 800 µg/ml was 98.31%, 85.46±0.035%, 81.39±0.065% and 70.80±0.075% respectively. The IC_{50} values shown by ascorbic acid, canagliglozin, dapagliflozin and empagliflozin were 141.8±0.09, 207.5 ± 0.10, 243 ± 0.23, 264.6 ± 1.07 (Table-4).

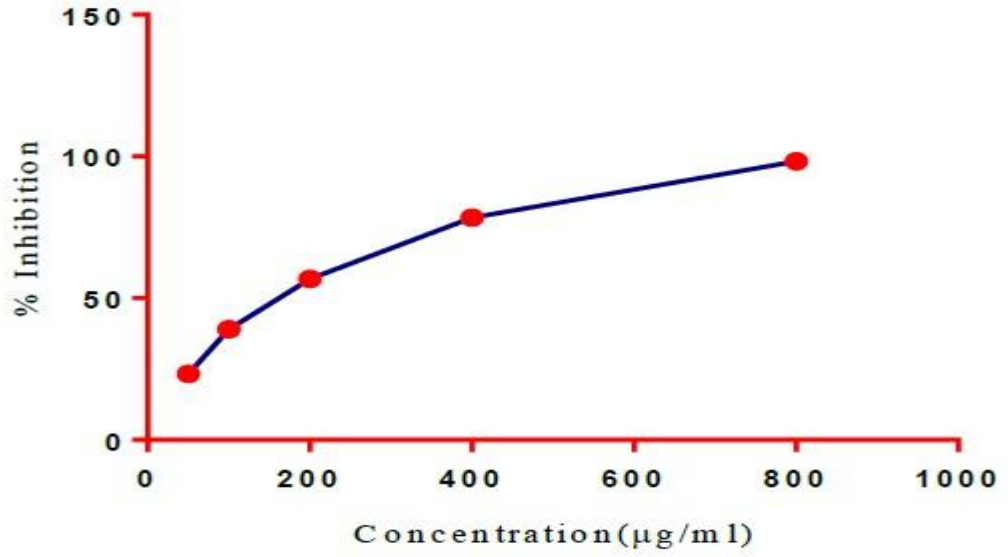

Figure 9: Standard curve of ascorbic acid in inhibition of LPO assay

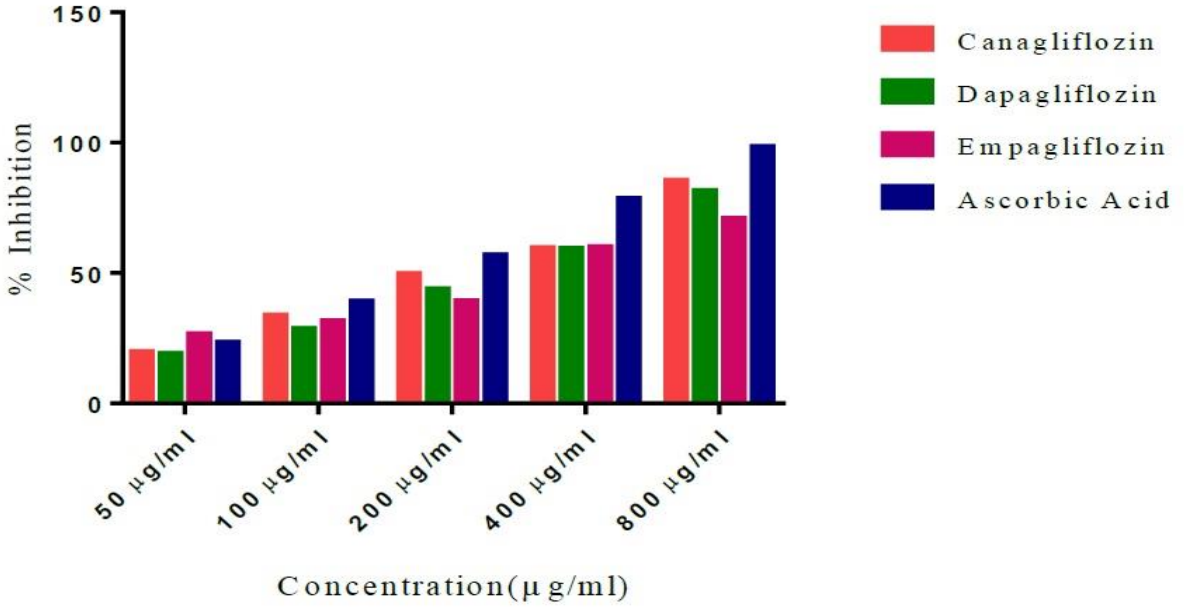

Figure 10: Antioxidant Potential of Gliflozin Analogues in inhibition of LPO assay

Statistical Analysis

All samples were analyzed in sextuplicate and data are reported as Mean ± SEM. Statistical analysis was done with GraphPad Prism version 7. IC_{50} values were calculated taking concentration versus normalized response with variable slope in nonlinear regression.

Table: 1 Free radical scavenging potential of Canagliflozin measured as % Inhibition

Concentration µg/ml	DPPH	Nitric Oxide	FRAP	Phospho-molybdenum	Lipid Peroxidation
50	38.52±0.040^{c}	28.42±0.060^{c}	14.53±0.045^{c}	6.78±0.110^{c}	19.63±0.135^{b}
100	48.25±0.065^{c}	32.72±0.075^{c}	20.92±0.060^{b}	25.41±0.075^{c}	33.74±0.125^{c}
200	59.86±0.055^{b}	38.73±0.220^{c}	33.22±0.035^{ns}	40.06±0.055^{c}	49.57±0.075^{c}
400	73.54±0.075^{c}	50.31±0.310^{c}	51.10±0.110^{c}	62.06±0.060^{c}	59.51±0.110^{c}
800	87.18±0.080^{c}	66.77±0.140^{c}	74.18±0.080^{c}	98.63±0.045^{a}	85.46±0.035^{c}

Data are expressed as mean ± standard deviation (n = 4); mean in the same column with different superscripts are significantly different using unpaired two-tailed t-test at p <0.05.

a = * p < 0.05, b = ** p < 0.01, c = *** p < 0.001, ns = nonsignificant p > 0.05

Table 2: Free radical scavenging potential of Dapagliflozin measured as % Inhibition

Concentration µg/ml	DPPH	Nitric Oxide	FRAP	Phospho-molybdenum	Lipid Peroxidation
50	27.62±0.030^{c}	36.54±0.050^{b}	14.54±0.030^{c}	3.22±0.040^{c}	18.98±0.055^{b}
100	38.32±0.025^{c}	41.23±0.085^{c}	21.55±0.060^{c}	6.90±0.085^{c}	28.62±0.070^{c}
200	61.24±0.040^{c}	47.75±0.110^{c}	38.08±0.040^{c}	20.97±0.055^{c}	43.82±0.090^{c}
400	80.62±0.025^{c}	53.90±0.075^{c}	52.70±0.085^{c}	55.57±0.115^{c}	59.35±0.070^{c}
800	97.47±0.010^{b}	68.23±0.080^{c}	90.22±0.105^{c}	98.07±0.110^{a}	81.39±0.065^{c}

Data are expressed as mean ± standard deviation (n = 4); mean in the same column with different superscripts are significantly different using unpaired two-tailed t-test at p <0.05.

a = * p < 0.05, b = ** p < 0.01, c = *** p < 0.001, ns = nonsignificant p > 0.05

Table 3: Free radical scavenging potential of Empagliflozin measured as % Inhibition

Concentration µg/ml	DPPH	Nitric Oxide	FRAP	Phospho-molybdenum	Lipid Peroxidation
50	37.37±0.015^{c}	46.70±0.055^{c}	11.41±0.080^{ns}	3.15±0.060^{c}	26.58±0.070^{b}
100	40.94±0.020^{c}	50.20±0.020^{b}	24.53±0.065^{c}	16.78±0.105^{c}	31.51±0.055^{c}
200	43.20±0.010^{c}	54.08±0.110^{c}	34.61±0.080^{a}	37.08±0.04^{c}	39.24±0.075^{c}
400	51.88±0.015^{c}	61.08±0.135^{c}	59.38±0.115^{b}	59.34±0.075^{c}	59.93±0.045^{c}
800	60.83±0.030^{c}	72.80±0.115^{c}	94.70±0.085^{c}	99.30±0.085^{ns}	70.80±0.075^{c}

Data are expressed as mean ± standard deviation (n = 4); mean in the same column with different superscripts are significantly different using unpaired two-tailed t-test at p <0.05.

a = * p < 0.05, b = ** p < 0.01, c = *** p < 0.001, ns = nonsignificant p > 0.05

Table 4: Tabular Representation of IC_{50} Value of Drugs and Standard

Name	DPPH Scavenging	Nitric Oxide Scavenging	FRAP	Phospho-molybdenum	)ition of LPO
Ascorbic acid	117.4 ± 0.02	93.64 ± 0.115	271.2 ± 0.06	174.3 ±0.04	141.8±0.09
Canagliflozin	103.6 ± 0.06^{c}	331.5 ± 0.16^{c}	350.6 ±0.09^{c}	241.4 ±0.04^{c}	207.5 ± 0.10^{c}
Dapagliflozin	130.1 ± 0.06^{c}	210.9 ± 0.19^{c}	281.1 ±0.07^{c}	344 ±0.11^{c}	243 ± 0.23^{c}
Empagliflozin	294.1 ± 0.04^{c}	92.71 ± 0.06^{a}	264.1 ±0.16^{c}	272.3 ±0.07^{c}	264.6 ± 1.07^{c}

Data are expressed as mean ± standard deviation (n = 4); mean in the same column with different superscripts are significantly different using unpaired two-tailed t-test at p <0.05.

a = * p < 0.05, b = ** p < 0.01, c = *** p < 0.001, ns = nonsignificant p > 0.05

DISCUSSION

2,2-diphenyl-1-picrylhydrazyl (DPPH) is a stable nitrogen centred free radical widely used in the screening of antioxidant assay. Every antioxidant has some reducing property that can cause reduction of DPPH. After accepting one electron, hydrazyl group is converted to hydrazine and the deep violet colour of DPPH radical changes to light yellow, absorbance of which is measured at 517 nm. The decrease in absorbance indicates scavenging of DPPH free radicals by the antioxidant. All the gliflozin contains 4 electron-rich hydroxyl group and at least one oxane ring. Due to this electron availability, gliflozins should have good antioxidant activity which is shown in table 1. The IC_{50} value of canagliflozin is lower than ascorbic acid which indicates canagliflozin as better antioxidant than the standard.

The source of nitric oxide in human body is L-arginine and nitric oxide synthase[13]. In the structure of nitric oxide radical, the oxygen atom has a single unpaired electron. Scavengers of NO compete for cellular oxygen with L-arginine and reduce the production of NO free radicals. The secondary process of generation of nitric oxide free radical is reaction between peroxy radical and NO[14]. Nitric oxide radical ultimately causes ischemia reperfusion, neurodegenerative disease like multiple sclerosis, and chronic inflammatory disease. Nitric oxide binds to the double bonds of carbon skeleton in lipid structure, and replace the hydrogen with its oxygen atom by breaking relatively weak carbon hydrogen bond. The oxygen atom forms peroxide compound which in turns generate more free radicals. Peroxidation in presence of nitric oxide generates a metabolite peroxynitrite ($ONOO^{-}$) which is extremely reactive free radical. Peroxynitrite directly induce cytotoxic reactions like SH- group oxidation, lipid peroxidation, tyrosine nitration and DNA damage. Empagliflozin have the maximum number of electron lone pair in its structure, evidently it should have highest radical scavenging activity which is supported by table 1.

FRAP method is a measurement of reducing power of a compound. Empagliflozin showed the best reducing power in this method. Dapagliflozin have almost equal reducing power as standard ascorbic acid. The greater the reducing power, the greater will be the tendency to lose electron. Loss of electron from a compound makes it oxidised, thus the drugs have well enough capability to prevent oxidative stress.

Phosphomolybdenum assay measures the ability of drug to convert the yellow coloured complex phosphate-molybdate (VI) to green coloured complex phosphate-molybdate (V). This conversion involves a reduction reaction and so, phosphomolybdenum assay is a measure of the reducing power of the drug. Canagliflozin showed the best result, although significantly different from the standard ascorbic acid. However, the other drugs that should have shown better results showed significantly different results from

ascorbic acid. This may be due to the reaction rate of drugs and the phosphate-molybdate complex.

Ferrous sulphate is used in egg yolk homogenate to induce lipid peroxidation. Free radicals generated in the system attack the carbon chain of the lipid and breaks it giving rise to malondialdehyde (MDA) and several aldehydes. These aldehydes form a pink chromophore with thiobarbituric acid. Reaction between thiobarbituric acid and the aldehydes is stopped by addition of trichloroacetic acid. In physiological system, MDA is the marker of lipid peroxidation. MDA is a highly reactive carbonyl compound that forms adducts with amino group of proteins and biomolecules. MDA also forms adducts with DNA base pairs which are mutagenic as well as carcinogenic. Drugs that effectively prevent the lipid peroxidation in egg yolk homogenate is expected to prevent peroxidation of brain phospholipid also. Canagliflozin showed a good potential to inhibit lipid peroxidation, although the extent of inhibition of lipid peroxidation of canagliflozin is little lower than ascorbic acid.

The study indicates canagliflozin as the best inhibitor of lipid peroxidation and the antioxidant activity of canagliflozin is highest amongst the gliflozin analogues when measured by DPPH radical scavenging assay and phosphomolybdenum assay. The empagliflozin have the best antioxidant activity when measured by FRAP method and it is the best nitric oxide radical scavenger. Dapagliflozin have significant antioxidant activity as shown by DPPH radical scavenging assay and FRAP assay. So, canagliflozin and empaglifozin, when are in use clinically, they may elevate the quality of health of the patient by decreasing the diabetes induced oxidative stress and related complications. There may be a significant variation of these results in vivo as the therapeutic antidiabetic dose of the three drugs are different-canagliflozin 100 mg, dapagliflozin 10 mg and empagliflozin 25 mg[15]. So, the plasma drug concentration at normal therapeutic dose may vary and the antioxidant activity may also vary. Plasma protein binding is also a factor that may affect the in vivo results. The protein binding of canagliflozin is >99%[16], 91% of dapagliflozin[17] and 86.2% of empagliflozin[18]. The difference in plasma protein binding may affect the drug concentration in plasma and subsequently, the antioxidant activity. Further confirmation is required by investigating the in vivo antioxidant activity of these drugs.

CONCLUSION

The oxidative stress is a key factor for the propagation of diabetic neuropathy, diabetic retinopathy, diabetic nephropathy and other microvascular and macrovascular disease. All the three drugs i.e. Canagliflozin, Dapagliflozin, and Empagliflozin have promising antioxidant activity as compared to the standard antioxidant ascorbic acid. It can be suggested that empagliflozin and dapagliflozin can be employed clinically in oxidative stress induced diabetic complications besides their regular therapeutic approach. Moreover, some gliflozins analogues can contribute or enhance some of the potentiality of their efficacy by scavenging specific classes of toxic free radicals generated throughout the chronic diabetic stage.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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