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Contributed Paper

Synthesis, Docking Studies and Pharmacological Activity of Synthetic Flavonols

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ABSTRACT

Diabetes is a group of metabolic disorders characterized by hyperglycemic condition from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is coupled with long-term dysfunction, damage and even failure of different vital organs, like kidneys, nerves, eyes, heart and the blood vessels. Biologically flavonol derivatives were synthesized via Claisen-Schmidt condensation of ketones with different aldehydes in a good yield (%) for their antidiabetic potentials. The structures were established by different spectroscopic techniques like ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. The findings showed that substituted flavonols showed significant *in-vitro* enzyme inhibitions, molecular docking and *in-vivo* antidiabetic activities are potential candidates for the treatment of diabetes. The electron donating attached methyl derived flavonol (**OF2**) showed promising activity on □ -amylase (IC_{50} = 59.96±2.09 µg/mL respectively) in comparison with electron withdrawing group halogen to flavonol (**OF3,** IC_{50} = 70.19±2.26 µg/mL respectively) and simple flavonol (**OF1**) with (IC_{50} = 71.34±1.63 µg/mL). Administration of the **OF1** at a dose of 100 mg/kg caused a significant (**P < 0.01, n = 8) reduction in the level of blood glucose compared to diabetic control on 15th, 21st and 28th day. **OF2** in a dose of 100 mg/kg decreased blood glucose level from 253.8 to 180.7 mg/dl from 7th day onwards to 28th day (**P < 0.01, n = 8 for 7th and 15th day and ***P < 0.001, n = 8 for 21st and 28th day). The effect of **OF3** was almost similar to **OF1**.

Keywords: flavonol derivatives, α-amylase and α-glucosidase inhibition, molecular docking, streptozotocin, diabetes

1. INTRODUCTION

Diabetes mellitus (DM) is the common most metabolic disorder with gradually rising prevalence worldwide [1]. DM is an endocrine disorder with chronic hyperglycemia characterized by impaired insulin secretion or resistance [2]. Approximately 4% of the worldwide population is affected by DM and estimated to increase by 5.4% in 2025 [3]. Pancreatic alpha-amylase and alpha-glucosidase are significant intestinal enzymes for the digestion of starch yielding glucose and maltose with increased postprandial level of glucose. Inhibition of these enzymes will reduce starch digestion, a best way of diabetes management [4].

For achieving better glycemic control, oral antidiabetic agents including glucosidase inhibitors are used for therapeutic activity [5]. There are many herbal extracts having reported anti-diabetic potentials [6]. Among these phytochemicals, flavonoids and their related natural compounds are known to possess anti-diabetic activity, established in various animal models [7]. Flavonoids are the most common polyphenolic compounds used as medicaments for diabetes mellitus since ancient times [8]. Flavonoids represent about 6,000 phenolic compounds originate from herbs, fruits, cocoa, soy, chocolate, tea, red wine, vegetables and other plant food and beverage products, some of them exhibit excellent α-glucosidase and α-amylase inhibitory properties [9].

The above research data put emphasis on further research work on flavonol derivatives. Here in the first objective was to report synthesis of flavonoid derivatives and its antidiabetic evaluation. The second objective was to establish the structure activity relationship (SAR) of the flavonol derivatives.

2. MATERIALS AND METHODS

2.1 Chemicals

Ketone and benzaldehyde derivatives, silica, enzymes including α-amylase, α-glucosidase and substartes were of Sigma Aldrich Chemical Company. TLC plates were of Merck 60 F_{254}, Darmstadt Germany. Solvents and chemicals like ethanol, n-hexane, ethyl acetate used were of extra pure analytical grade were purchased from E. Merck.

^{1}H NMR and ^{13}C NMR spectra were recorded in deutrated chloroform (CDCl3) on Bruker SF spectrometers operating at 300 and 75 megahertz (MHz) frequencies respectively. Infrared spectra were recorded on Thermoscientific USA (Nickolet 6700), Infrared spectrometer on KBr disk method. All melting points are uncorrected and were taken in open capillary tubes using Electrothermal 9100 apparatus (Barnstead UK).

2.2 Chemistry

2.2.1 Synthesis and characterization of 3-hydroxyflavone derivatives

General procedure:

The 2'-hydroxychalcone was suspended in ethanol, and addition of NaOH (5 M, 2 eq) and H_2O_2 (30%, 2.2 eq) was carried out at 4 °C. The mixture was stirred at room temperature for 3-6 hours, afterwards acidified with HCl (2M) and poured into water (250 ml). Upon filtration, the precipitate was collected and recrystallized from methanol for obtaining pure product [10].

3-Hydroxy-2-phenyl-4H-chromen-4(1H)-one (OF1):

White crystals (R_f 0.63, 71%). Mp: 163-167 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.24 (d, 2H), 8.14 (1H), 7.83-7.81 (m, 1H), 7.79 (d, 1H), 7.59 (dd, 2H), 7.49-7.54 (m, 2H),

2.51 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.9, 121.8, 125.1, 125.3, 128.1, 129.0, 130.4, 131.8, 134.2, 139.6, 145.7, 155.1, 173.5. Anal. calcd for $C_{15}H_{10}O_3$: C 75.62, H 4.23%; found: C 75.62, H 4.09% [11].

3-Hydroxy-2-(4-Tolylphenyl)-4H-chromen-4(1H)-one (OF2):

Yellow crystals (R_f 0.70, 71%). Mp: 193-197 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.16 (d, 2H), 8.14 (1H), 7.79-7.82 (m, 1H), 7.79 (d, 1H), 7.47-7.50 (m, 1H), 7.40 (d, 2H), 2.56 (br s, 1H, OH), 2.41 (s, 3H, CH3). ^{13}C NMR (75 MHz, $CDCl_3$) 173.4, 155.1, 145.9, 140.3, 139.4, 134.1, 129.6, 129.1, 128.1, 125.3, 125.0, 121.7, 118.9, 21.5. Anal. calcd for $C_{16}H_{12}O_3$: C 75.37, H 4.86%; found: C 75.38, H 4.47% [11].

2-(4-Chlorophenyl)-3-hydroxy-4H-chromen-4-one (OF3):

White crystals (R_f 0.68, 74%). Mp: 198-201 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.33-8.19 (m, 2H), 7.75 (ddd, 1H), 7.67-7.40 (m, 3H), 7.35-7.05 (m, 2H), 2.44 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.43, 155.36, 136.20, 133.85, 131.65, 129.56, 129.02, 128.91, 127.66, 125.52, 124.68, 120.56, 118.27. FT-IR (KBr) : 3271.65 (OH-Aromatic), 1604.02 (C=O) cm^{-1}. Anal. calcd for $C_{15}H_9ClO_3$: C 66.07, H 3.33%; found: C 66.28, H 3.41% [12].

2.3 Biological Activities

2.3.1 *In-vitro* enzyme inhibition activity

The enzyme inhibition potentials of flavonols were assessed against α-amylase an α-glucosidase to determine the possible *in-vitro* antiabetic potentials of these compounds. The synthesized flavonols at various concentrations and standard (at various concentrations) was assessed for possible antidiabetic activity using in-vitro α-amylase and α-glucosidase inhibition activity by spectrophotometric analysis. Each experiment was repeated three times and the IC_{50} (i.e., the concentration of sample inhibiting 50% of α-amylase and α-glucosidase activity under the stated assay conditions) data of flavonols and standard are calculated [13, 14].

2.3.2 Drugs and animals

Tween-80 was purchased from Daejung Chemicals, Korea. Streptozotocin were of Sigma Aldrich Chemical Company. The standard glibenclamide was kindly provided by local industry. The healthy wistar male albino rats (180-210g) were purchased from National Institute of Health (NIH) Islamabad. The animals were housed in individual cages at the animal house of University of Malakand with free access to water and standard diet and starved for 12-18 hours before experimentation. Ethical Committe of the Department of Pharmacy, University of Malakand approved the experimental protocols and ensured its compliance with provisions of the "Animal Bye-Laws 2008, Scientific Procedures Issue-I of the University of Malakand".

2.3.3 Acute toxicity

The synthesized flavonols were screened for its possible toxicological effects using mice as model. The synthesized compounds were administered in two phases at different dose concentration and toxicological effects were assessed [15].

2.3.4 *In-vivo* antidiabetic activity

The *in-vivo* antidabetic activity was determined using streptozotocin diabetic model. In the experiment totally 48 rats (8 normal and 40 STZ diabetic surviving rats) were used. The GI (normal control), GII (diabetic control), GIII (standard glibenclamide, 600 µg/kg) and GIV-VI

were OF1, OF2 and OF3 (100mg/kg b.w) respectively. Blood glucose estimation was done using a glucometer on 1, 5, 7, 15, 21 and 28 days after treatment. Lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride) and activities of SGPT and SGOT were assayed in the serum [16].

2.4 Molecular Docking

The docking is a significant tool to explore the interactions between an inhibitor (molecule) and the target [17]. To find the binding interactions of these compounds in the active sites α-glucosidase and α-amylase, the MOE-Dock program was used to perform molecular docking. The crystal structure of α-glucosidase is not available yet, so, we used homology model as described by Ming Liu et al [18] while the 3D crystal structure of the α-amylase (1HNY) was retrieved from the Protein Databank (PDB). The structures of the flavonol derivatives were built in MOE and energy minimized using the default parameters of the MOE. Both α-glucosidase and α-amylase were allowed to dock to the flavonol compounds using MOE by the default parameters i.e., Placement: Triangle Matcher, Rescoring: London dG. For each ligand ten conformations were generated. The top-ranked conformation of each compound was used for further analysis.

2.5 Statistical Analysis

Data are presented as mean ± SEM. Analysis of variance and Dunnett's test is statistically manipulated with *Prism version 5.01* for Windows (*GraphPad Software*, *San Diego*, CA, *USA*).

3. RESULTS AND DISCUSSIONS

3.1 Chemistry

The physical parameters (color, appearance, R_f value, yield and mp) and characterization of the synthesized flavones and flavonols are given in methodology of synthesis. The route of the title compounds is given in Figure 1.

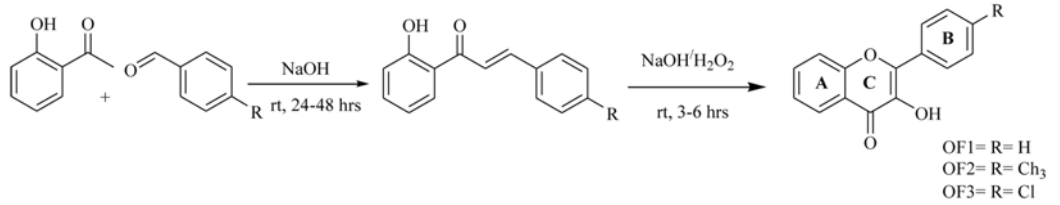

Figure 1. Synthetic route of the title compounds (OF1-OF3).

The compound **3-Hydroxy-2-phenyl-4H-chromen-4-one (OF1)** has already been reported and by comparing our spectroscopic data with the published literature we have strong confirmation regarding its structure. In case of **OF1**, we noticed a total of nine (9) protons in in the aromatic region, i.e. 7.54-8.24 ppm. The alpha hydrogen of OH group at position 3 appeared as distinct singlet at chemical shift of 2.51. In case of **3-Hydroxy-2-(4-Tolylphenyl)-4H-chromen-4(1H)-one (OF2)**, the protons (8) in the aromatic region, i.e. 7.40-8.16 ppm. The alpha hydrogen of OH group at position 3 appeared as distinct singlet at chemical shift of 2.56. Moreover, the singlet of 3H is observed at 2.41 ppm confirming the presence of methyl group.

Similarly for **2-(4-Chlorophenyl)-3-hydroxy-4H-chromen-4-one (OF3)**, the protons in the aromatic region, i.e. 7.05-8.33 ppm were obsereved with alpha hydrogen of OH as distinct singlet at chemical shift of 2.44. The synthesized flavonols **OF1** to **OF3** has already been reported and by comparing our spectroscopic data with the published literature we have strong confirmation regarding its structure [11, 12].

3.2 *In-vitro* Activities

3.2.1 *In-vitro* enzyme inhibition

The *in-vitro* enzyme inhibition potentials capacity of the flavone derivatives on α-amylase and α-glucosidase was determined and IC_{50} values are given in Table 1. It is evident that electron donating attached methyl derived flavonol (**OF2**) showed promising activity on α-amylase (IC_{50}=59.96±2.09 µg/mL respectively) in comparison with and simple flavonol (**OF1**) with (IC_{50}=71.34±1.63 µg/mL respectively). On the other hand, the inclusion of electron withdrawing group halogen to flavonol (**OF3,** IC_{50}=70.19±2.26 µg/mL respectively) almost similar result was observed to that of simple flavonol **OF1**.

Table 1. *In-vitro* enzyme inhibition potentials of flavonol derivatives.

Sample Test	Enzyme inhibition (IC_{50} µg/ml)	
	α-amylase	α-glucosidase
OF1	71.34±1.63	53.65±1.96
OF2	59.96±2.09	40.48±1.87
OF3	70.19±2.26	51.38±2.31
Quercetin	44.82±2.72	31.96±2.48
Acarbose	88.18±2.65	68.22±3.05

All the values were expressed as mean ±SEM (n=3).

The *in-vitro* enzyme inhibition potentials capacity of the flavonol derivatives on α-glucosidase was determined and IC_{50} values are also given in Table 1. Almost similar type of results were observed for synthesized flavones and flavonols suggesting the inclusion of electron donating and withdrawing groups have enhanced inhibitory effects (IC_{50} values) than that of simple flavonol.

By comparing the results of antioxidant and *in-vitro* enzyme inhibition activity, it was observed that the methyl containing flavonoid derivatives showed promising results and suggest the possible role of methyl containg flavonoids as possible antiabetic agents.

3.2.2 *In-vivo* antidiabetic activity

In the *in-vivo* acute toxicity studies of the synthesized flavonol derivatives, there were no observation of gross physical and behavioral changes for 24 hours and no mortality occurred within the observation period of 14 days.

Since the compounds even at a dose of 1000 mg/kg didn't show any mortality rate in mice so it is consider to be comparatively safe, during the study it was observed that the systemic administration of the compounds didn't produced any sedation, alteration in locomotor activity or motor dysfunction in animals.

Changes in blood glucose level in control (normal), control (diabetic) and diabetic treated with flavonol derivatives and standard glibenclamide are presented in Figure 1. Administration of the **OF1** at a dose of 100 mg/kg caused a significant (**P<0.01, n=8) reduction in the level of blood glucose compared to diabetic control on 15th, 21st and 28th day. **OF2** in a dose of 100 mg/kg decreased blood glucose level from 253.8 to 180.7 mg/dl from 7th day

onwards to 28th day (**P<0.01, n=8 for 7th and 15th day and ***P<0.001, n=8 for 21st and 28th day). The effect of **OF3** was almost similar to **OF1**. The antidiabetic effect of **OF1-OF3** was comparable to that of glibenclamide a standard antidiabetic agent.

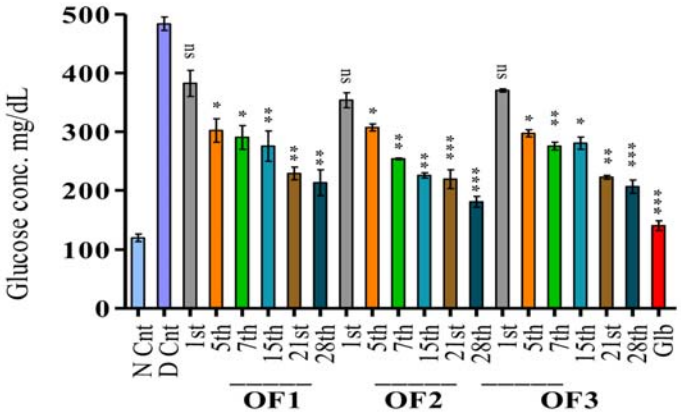

Figure 1. Antidiabetic potentials of flavonols.

The lipid profiles and the activity of hepatic marker enzymes in serum in control and experimental rats are shown in Table 2. Administration of the flavonols **OF1-OF3** for 28 days showed a substantial (*P<0.05,**P<0.01, n=8) reduction in total cholesterol, TGs and LDL cholesterol in comparison to diabetic control rats. The effect was comparable to that of glibenclamide (600 □g/kg) used as a standard drug. Administration of flavonols considerably reduced (*P<0.05, **P<0.01, n=8) serum SGPT, and SGOT in rats intoxicated with STZ that was comparable to standard drug glibenclamide (**P<0.01, n=8).

Table 2. Antihyperlipidemic effect of flavonols on STZ induced diabetic rats.

Groups	Dose mg/kg	Total CH (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)	(SGPT) IU	(SGOT) IU
Normal control	0.4 ml	129.5±5.7	43.8±4.8	90.5±4.3	137.4±5.5	19.6±4.7	21.8±4.6
Diabetic control	0.4 ml	194.2±5.4**	39.5±4.1*	184.6±4.9**	178.2±5.2**	59.7±3.4	46.5±4.5**
Glibenclamide	0.6	148.1±6.3**	44.7±5.4**	94.6±5.5***	142.5±4.9**	22.6±5.1**	24.7±4.8**
OF1	100	161.3±4.9*	49.2±6.2*	112.4±4.7*	155.6±3.7**	31.4±5.1*	25.7±4.3**
OF2		150.7±3.9**	43.5±3.8**	98.8±4.3**	146.9±4.6*	26.4±5.2**	20.1±4.9*
OF3		154.3±5.6	52.9±4.8	107.6±3.8	153.8±5.4	33.5±4.8	27.4±5.2

All the values were expressed as mean □ SEM (n=8). One way ANOVA followed by Dunnett's multiple comparison tests was performed. Values *P<0.05, **P<0.01, ***P<0.001 was considered to indicate statistical significance when compared to control.

3.2.3 Docking analysis of α-glucosidase

In order to explore the binding mode of these flavonol derivatives, molecular docking was performed. From the molecular docking studies, it was observed that the topranked conformation of all the compounds fit well inside the active site of the homology model of α-glucosidase (Arg 212, Asp214, Glu276, Asp 349 and Arg 439). From the docking conformation of the compounds, it was revealed that compound **OF2** (IC_{50} = 40.48±1.87 µg/mL, docking score = -9.2112) formed five hydrogen bonds, one arene-cationand one arene-arene linkages with the Phe 177, Arg 212, Asp 214, Glu 276, His 348 and Arg 439 residues of the binding pocket of the α-glucosidase as shown in Figure 2. Arg 212, Asp 214 and His 348 formed a polar interactions with the oxygen atom of carbonyl of the compound. Arg 212 and Glu 276 formed H-bonds with hydroxyl moiety of the compound while Phe 177 and Arg 439 were observed making π-π and arene-cation interactions with the benzene moiety of the same ligand. The presence of the electron donating groups (-OH and -CH3) and electronic cloud system of this compound might be the reason of its high potency.

Table 3. Docking score of flavonol derivatives.

Sample Test	Docking score	
	α-amylase	α-glucosidase
OF1	-7.3166	-8.2935
OF2	-8.7705	-9.2112
OF3	-7.4322	-8.9858
Quercetin	-8.3219	-9.3201
Acarbose	-7.0102	-7.9983

The third one active compound in the Table 1 is **OF3** (51.38±2.31 µg/mL**)** which was observed having good interaction as well as docking score (-8.9858) in Table 3. Glu 276 residue made H-bond with hydroxyl moiety of the compound while His 348 formed polar interaction with the carbonyl oxygen atom of the same compound as shown in Figure 2. The availability of the electron donating groups (-OH), electron withdrawing (-Cl) and π electrons, make the compound polarizable and potent. Overall a good correlation was observed between the docking study and biological evaluation of active compounds.

3.2.4 Docking analysis of α-amylase

The docking results of the compounds with the α-Amylase enzyme have given good information about the nature of the binding mode that was excellent correlated with the experimental results. The docking results revealed the best accommodation of compounds in the active site residues (Trp 58, Trp 59, Tyr 62, Leu 162, Arg 195, Asp 197, Glu 233, Asp 300 and His 305) of the target enzyme. From the conformation of compound **OF2** (docking score= **-8.7705,** Table 3) it was observed to formed two hydrogen bonds and one arene-arene linkage with the active site residues of α-amylase.Trp 59 was observed in making π-π interaction with the benzene moiety of the compound while Asp 300 and His 305 established interactions with -OH group and oxygen atom of carbonyl respectively of the compound **OF2** as shown in Figure 2. The high potent inhibitory activity may be due to the presence of the electron accepting group (carbonyl oxygen) and electron donating groups (-OH and methyl group) which create an electron flow making the compound more active, polarizable and potent.

Compound **OF3** (docking score = -7.4322) was observed having one polar interaction with the Asp 300 residue of the binding pocket of the enzyme as shown in Figure 2. Trp 59 formed arene-arene contact with bezene moiety and Asp 300 made H-bond with the -OH group of the same compound. The inhibition of this compound might be due to the availability of the electron withdrawing group (-Cl).

All the compounds displayed good docking results which correlate with the biological results.

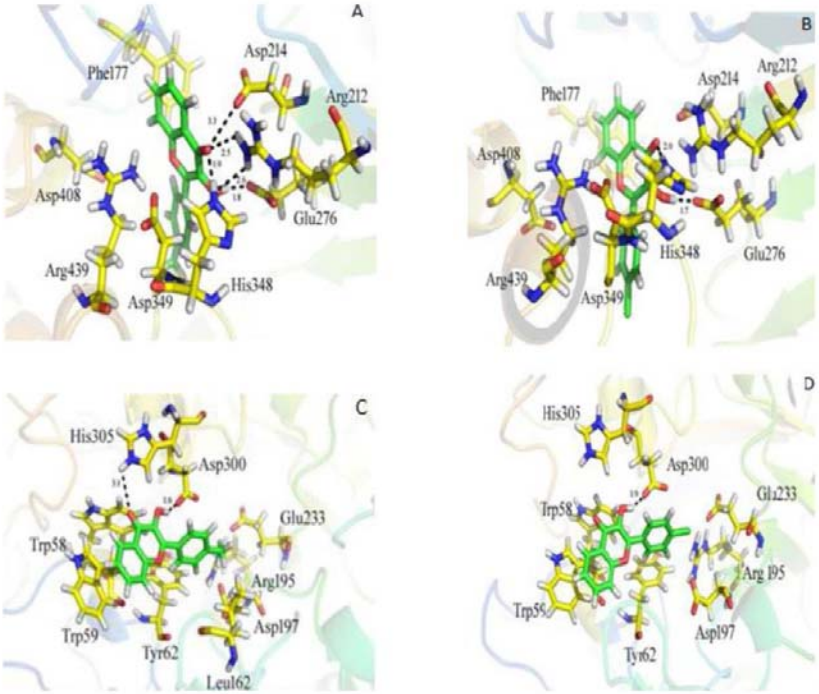

Figure 2. Docking conformation of compound OF2 in the active site of α-glucosidase, A (OF2), B (OF3) and of α-amylase C (OF2) and D (OF3).

Diabetes mellitus (DM) is a well-known, progressive endocrine disorder coupled with increase in morbidity and mortality, in association with high cost in health care. There were approximately 171 million cases of DM in 2000, and this number is expected to more than double over the next 25 years, reaching 366 million by 2030 [19]. This increasing trend has become a serious worldwide medical concern that stimulates the search for new therapeutic agents. Common clinical features of DM are hyperglycemia, alterations in the metabolism of protein, carbohydrates and lipids due to defects in the production or action of insulin [20]. Diabetes is characterized by postprandial hyperglycemia which occurs in early stages leading to several secondary complications, like high risk of cardiovascular diseases, atherosclerosis, cataracts, retinopathy, neuropathy, nephropathy and impaired wound healing [20].

Diabetes mellitus is a clinical syndrome with severe socioeconomic importance characterized by hyperglycemias due to absolute or relative lack of insulin [21]. Among the strategies adopted for the treatment of diabetes mellitus include

enzyme inhibition such as α-amylase and α-glucosidase in gastrointestinal tract used for carbohydrate-digestion, leading decreased intestinal glucose absorption and lowering of postprandial blood glucose levels. The α-glucosidase cause the cleavage of glycosidic bonds releasing absorbable monosaccharides. Therefore, the α-glucosidase inhibitors exhibit valuable anti-hyperglycemic effects [22]. The purpose of current study is to determine the *in-vitro* antioxidant activities of synthetic flavones and flavonols and the assessment of α-amylase and α-glucosidase inhibitory activity of these molecules for determining its possible antidiabetic potentials. Previous studies confirm the role of medicinal chemistry (synthesis and pharmacology) in the development of lead antioxidant and antidiabetic agents in the form of α-amylase and α-glucosidase inhibitors [23-25].

α-amylase is the key enzyme in human body responsible for starch breakdown into more simpler sugar. The complex polysaccharides are hydrolyzed to oligo and disaccharides by α-Amylases and then α-glycosidase hydrolyze it to absorbable monosaccharide in the small intestines and enter into hepatic portal vein, consequently increasing the postprandial glucose levels [26]. Amylase inhibitors are also termed as starch blockers as it prevent the absorption of dietary starch thereby lowers postprandial glucose levels. By slowing the breakdown and digestion of starch may have useful effects on insulin resistance and glycemic index control in diabetic people [27]. Ingesting a carbohydrate-rich diet triggers elevated blood glucose levels due to the rapid absorption of carbohydrates, which is aided by glycoside hydrolases, such as alpha-glucosidase (EC 3.2.1.20); this enzyme is present in the epithelial mucosa of the small intestine and cleaves the glycosidic bonds in complex carbohydrates to release absorbable monosaccharides [28]. The α-glucosidase cause the cleavage of glycosidic bonds releasing absorbable monosaccharides. Therefore, the α-glucosidase inhibitors exhibit valuable anti-hyperglycemic effects [22]. Using α-glucosidase inhibitors has become a promising therapeutic strategy for reducing the risks of diabetes and other carbohydrate-mediated diseases, including hyperlipoproteinemia and obesity [29].

According to our investigation, flavones and flavonols causes moderate to high inhibition of α-amylase and α-glucosidase. It has been reported that naturally occurring polyphenols possess the activity to inhibit the enzyme like α-amylase, α-glucosidase responsible for hydrolyzing carbohydrate [26].

Therefore, this study buttress the claim that flavonoids either from natural or synthetic source have α-amylase and α-glucosidase inhibitory activity and could be used as effective therapy for the management of postprandial hyperglycemia with minimal side effects [30].

4. CONCLUSIONS

Researchers are constantly designing and synthesizing the new molecules and the present study is an effort to assess flavonol derivatives as potential drug candidates for lead molecules. The SAR study revealed a correlation between the presence of additional groups during *in-vitro* enzyme inhibiting and *in-vivo* antidaibetic potentials to act as future potential candidates to develop newer synthetic antidiabetic agents.

In conclusion, the present study confirms the *in-vitro* enzyme inhibition and *in-vivo* antidiabetic activities of flavonols. These findings will open a new channel to synthesize and explore the development of synthetic

molecules for the treatment of wide range of diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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