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An allied approach for *in vitro* modulation of aldose reductase, sorbitol accumulation and advanced glycation end products by flavonoid rich extract of *Coriandrum sativum* L. seeds

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ABSTRACT

Traditional herbal medicines are attaining more popularity and are being widely practiced. *Coriandrum sativum* L. is one of the oldest herbal medicinal plants valued for its nutritional and medicinal properties. Present investigation was focussed on evaluation of attenuating potential of flavonoid rich extract of *C. sativum* (FCS) seeds against pathogenic markers of diabetic complications *i.e.* advanced glycation end products (AGEs), sorbitol and aldose reductase (ALR); by using *in-vitro* methods. Gas chromatography–mass spectrometry (GC–MS) and Infrared spectroscopy of FCS revealed the presence of different flavonoids.

Results demonstrated that FCS has produced 79.80% inhibition of AGEs formation. Additionally, FCS was effective against sorbitol accumulation and ALR inhibition with IC_{50} values of 221 μg/ml and 6.08 μg/ml respectively. Molecular docking was conducted against three binding site for ALR, RAGEs and sorbitol dehydrogenase to explore their binding interactions with identified flavonoids. The constituents F_2, F_4 and F_6 have shown good binding interactions with all the receptors. The visualisation of the docked complexes revealed the occurrence of hydrophobic forces and hydrogen bonding in receptor and docked constituents.

The results were in support with experimental inhibitory activities of FCS against these biomarkers and provide a considerable basis for the identification and development of new inhibitors.

1. Introduction

The emerging concept of functional foods promotes use of food as more than simply nutrition. In recent years, the rise of functional foods has played a key role in healthy habits due to growing concern about health and discernment that diet directly affects healthiness [1]. Briefly, functional foods are conventional or everyday foods composed of naturally occurring components and are consumed as part of the normal daily diet. Functional foods exert positive effects on target functions beyond their nutritive value, enhancing the well-being and quality of life, and reducing the risk of diseases [2,3].

Hyperglycemia arising from diabetes is responsible for generation of reactive oxygen species (ROS) which results to oxidative stress, increased formation of AGEs, over expression of their receptors (RAGEs) as well as activation of biochemical pathways including ALR-polyol pathway (reduction of glucose to sorbitol by ALR), PKC/DAG pathway etc [4,5]. AGEs like glucosepane, fructosamine may inflict sustained damage to the extracellular matrix in diabetes and in addition tissue stiffening, accelerated sclerosis in arteries, kidneys, and other organs come in effect [6]. Furthermore, ALR over utilizes NADPH (nicotinamide adenine dinucleotide phosphate) for sorbitol formation, leading to homeostatic imbalances and ultimately to oxidative stress. Sorbitol undergoes NADH dependent sorbitol dehydrogenase catalyzed fructose production. Fructose so formed leads to generation of carbonyl species which are key factors in formation of AGEs and ROS thus elicits oxidative stress. Excess of sorbitol and its metabolites start to accumulate in different cells and tissues and trigger the vascular damage. Hence, AGEs, ALR and sorbitol accumulation are dynamically involved in the pathogenesis of diabetic complications [4,7,8]. Based on these pivotal mechanisms, the medicinal agents are being investigated as prospective agents which can reduce AGEs formation and lower sorbitol concentrations by inhibiting ALR enzyme, therefore could allocate new

Abbreviations: PKC, protein kinase C; DAG, diacyl glycerol; NADPH, nicotinamide adenine dinucleotide phosphate; DPPH, 2,2-diphenyl-1-picrylhydrazyl; AG, aminoguanidine

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treatment possibilities for the complications of diabetes.

Coriandrum sativum L. belongs to Apiaceae family and is one of the oldest herbal plants valued for its nutritional and medicinal properties [9,10]. *C. sativum* contains multiple bioactive components like flavonoids, phenolic acids, terpenoids, fatty acids, tocopherols, vitamin c etc. [9,11], which contribute to its pharmacological effects including anti-diabetic, antioxidant, anti-inflammatory, and neuroprotective etc [12,13]. *C. sativum* fits into the concept of functional food as it is the most commonly used part of regular diet and above said possible beneficial pharmacological benefits promote its use as a functional food [13].

Flavonoids are considered as excellent free radical scavenging agents [14] which effectively protect against ALR activity [15–17] thereby, replenishing the depletion of NADPH levels known to envisage cytoprotective action against oxidative stress by modulating polyol pathway. Protein damage (Glycation) is also prevented by flavonoids through deactivation of PKC/DAG and AGEs pathways [17–19].

Many potent synthetic AGEs and ALR inhibitors have been offered but due to side effects, low efficacies and poor pharmacokinetics they were withdrawn from clinical trials [5]. These synthetic agents were anticipated as the prototypes for new and potent drugs, and many researchers have been working to find new, potent, and safe AGEs and ALR inhibitors from plant sources [8,20]. Following the trends related to safe natural products, including functional foods and their active constituents, present study was designed to investigate the flavonoid rich extract of *C. sativum* against the pathogenic markers of diabetic complications.

2. Materials and methods

2.1. Preparation of FCS and phytochemical screening

The plant material of *C. sativum* was procured from local agricultural market of Ambala, Haryana and authenticated by Dr. K. Madhava Chetty, Department of Botany, SVU, Tirupati. Plant specimen voucher no. 1078 is available in the institute's herbarium for future reference. 10 gm of *C. sativum* seeds were coarsely powdered and were extracted in triplicate with 100 ml aqueous alcohol (water and ethanol in ratio of 80: 20, v/v) at room temperature. The whole solution was filtered using Whatman filter paper no. 42. The filtrate was transferred to a crucible and evaporated to dryness and weighed to a constant weight and was used for further study. The phytochemicals present in the FCS were screened according to methods described by Dohou et al. and Senhadji et al. [21,22].

2.2. Total flavonoid content

The total flavonoid content FCS determined by the $AlCl_3$ colorimetric method using Rutin as standard [23]. The absorbance was taken at 415 nm using UV–Vis spectrophotometer. The concentration of flavonoid was expressed as mg of rutin equivalent (RE) per gram of FCS.

2.3. Thin layer chromatography (TLC)-bioautography

TLC was run using solvents Chloroform and methanol (8:2) for separating the constituents of FCS. Bioautography was performed to confirm the presence of antioxidant compounds in FCS according to method described by Hemalatha et al. [24]. The specific compounds which possess antioxidant properties shows clear zone of yellow colour against purple background developed by DPPH.

2.4. GC–MS analysis

Sample for GC–MS analysis was prepared according to the method described by Zhang and Zuo [25] with a slight modification. Sample was dissolved in methanol and filtered. Filtrate (10 ml) was extracted using methanol: chloroform: formic acid (7:2:1). The mixture was centrifuged for 10 min, and the top layer was removed and pooled in another tube. The extract was concentrated and mixed to 70 µl of the 2, 2, 2-trifluoro-*N*-Methyl-*N*-trimethylsilylacetamide (MSTFA) and heated for 2 h at 37 °C. Shaking was continued for another 30 min subsequently. Derivatised mixture was subjected to GC–MS. Initially column was maintained at 60 °C for 5 min after injecting the sample and temperature conditions were raised to 140 °C with a proportion of 10 °C min. Temperature was further increased to 200 °C with 5 °C min for 20 min. Final temperature of injector was 250 °C and for detector was 275 °C. H_2 was used as carrier gas. Inlet pressure 45 psi linear, gas velocity 39 cm/sec, column flow rate 2.4 mL/min, split ratio (40:1) and injector volume 1 µL.

2.5. Fourier transform infra-red (FTIR) spectroscopy

The pellets of FCS and KBr (potassium) were made in a hydraulic press and were subjected to FTIR analysis in range of 450-4000 cm^{-1} using FTIR-Shimadzu spectrometer.

2.6. Aldose reductase (ALR1) enzyme inhibition

Partial purification of ALR1 from rat kidney (IAEC Protocol No.: MMCP/IAEC/16/07) was carried out. The activity of ALR1 was measured spectrophotometrically by monitoring the oxidation of NADPH at 340 nm as a function of time at 37 °C using glyceraldehyde as substrate. The percentage inhibition was calculated considering the activity in the absence of FCS as 100%. The IC_{50} values were determined by linear regression analysis of the plot of percent inhibition versus inhibitor concentration [26].

2.7. Anti-glycation activity

In vitro antiglycation activity of FCS was examined by testing their ability to inhibit the fluorescence of bovine serum albumin for subsequent four weeks according to the method given by Matsuda et al. [27] using aminoguanidine as a standard. AGEs formation was measured by fluorescent intensity at an excitation wavelength 355 nm and emission wavelength 460 nm using Elico-SLI74 Spectrofluorometer.

2.8. Erythrocyte sorbitol accumulation inhibition

Heparinized human blood (5 mL) was collected from overnight fasted healthy male volunteer and erythrocytes were separated from the plasma by centrifugation according to the method described by Haraguchi et al. 1997 [28]. The relative fluorescence due to NADH was measured by a fluorescence spectrometer (Elico-SLI74 Spectrofluorometer) at an excitation wavelength of 366 nm and an emission wavelength of 452 nm. The experiments were performed in triplicates.

2.9. Molecular docking

Molecular docking was performed using VLife Molecular docking software version 4.6.10. ALR (PDB ID: 1AH3), RAGEs (PDB ID: 3CJJ) and sorbitol dehydrogenase (PDB ID: 1PL7) crystal structure was used for the molecular docking. The PDB was obtained from RCSB PDB-101 protein crystals database (PDB, http://www.rcsb.org/pdb/). All the water molecules were removed at the time of opening PDB in VLife MDS working surface. Ligand was prepared in ACS/ChemSketch 2010 and was saved as mol.2 file. Proteins were analysed for the active site and docked with ligands to get the binding energy/docking score. The interaction of docked complexes was viewed in "interactions" section of software.

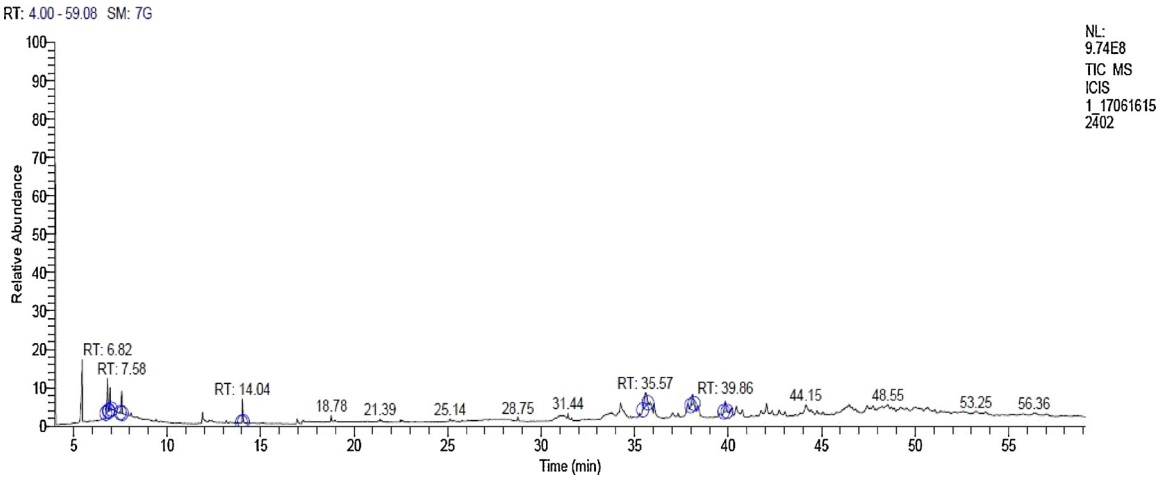

Fig. 1. GC–MS analysis results of FCS showing different peaks.

Fig. 2. TLC bioautograph of FCS showing presence of antioxidant compounds.

Table 1
Results of GC–MS analysis of flavonoid rich extract of *C. sativum* seeds (FCS).

Peak	Retention time	Area (%)	Database/NIST 14 library
1 (F_1)	6.82	20.71	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one
2 (F_2)	6.92	11.01	Quertcetin-3-O-rutinoside
3 (F_3)	7.58	12.08	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one
4 (F_4)	14.04	10.58	3,3',4',5,7-Flavanpentol
5 (F_5)	35.57	23.63	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromenone
6 (F_6)	39.08	11.38	7-O-methylquercetin
7 (F_7)	39.86	10.40	4',5,7-Trihydroxyflavone

3. Results and discussion

3.1. Phytochemical composition

Phytochemical screening revealed the presence of flavonoids and flavones. Results so obtained are in accordance with available literature evidencing the presence of flavonoid content in *C. sativum* [9]. FCS was further subjected to total flavonoid content determination by aluminium chloride method. A linear equation was obtained from the calibration curve of rutin to calculate the flavonoid content as mg of rutin equivalent to per gram of FCS. Total flavonoid content was found to be 127 mg of rutin equivalent to per gram of FCS.

FCS with a concentration of 1 mg/ml was run on TLC using chloroform and ethanol. Developed TLC plates were dried and then were sprayed with 0.2% DPPH. Reduction of DPPH radical to non-radical DPPHH was confirmed by visual change in colour from purple to yellow indicating the presence of antioxidant compounds (Fig. 1). Flavonoids are better known for their antioxidant potential; therefore bioautography results also evidenced the presence of flavonoids. Considering these results, FCS was further subjected to GC—MS analysis for confirmation of potential constituents. Peaks so obtained from GC—MS (Fig. 2) were interpreted according to data base of National Institute Standard and Technology (NIST-14) library. List of the identified compounds along with percent composition in FCS are presented in Table 1. Results revealed the presence of different flavonoids including rutin, quercetin, leutiolin etc. Furthermore, FCS was analysed by FTIR to identify functional groups in bioactive components. FTIR spectrum for FCS (Fig. 3) with its peak values were obtained at 617.77, 731.21, 746.35, 800.62, 868.13, 1019.35, 1045.43, 1102.08, 1180.85, 1375.39, 1417.93, 1494.96, 1577.17, 1613.10, 1719.37, 1743.36, 1842.84, 1864.45, 2227.48, 2281.16, 2319.33, 2393.01, 2511.07, 2732.14, 2854.66, 2924.35, 2956.17, 3049.79, 3170.36, 3326.43 cm^{-1}

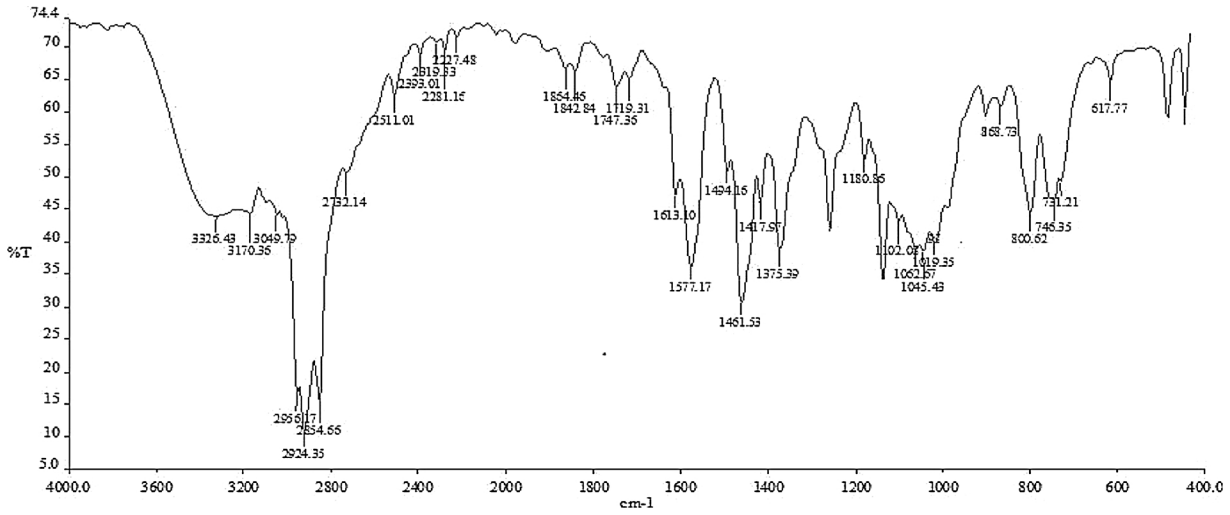

Fig. 3. IR spectra of FCS showing presence of different functional groups of active constituents.

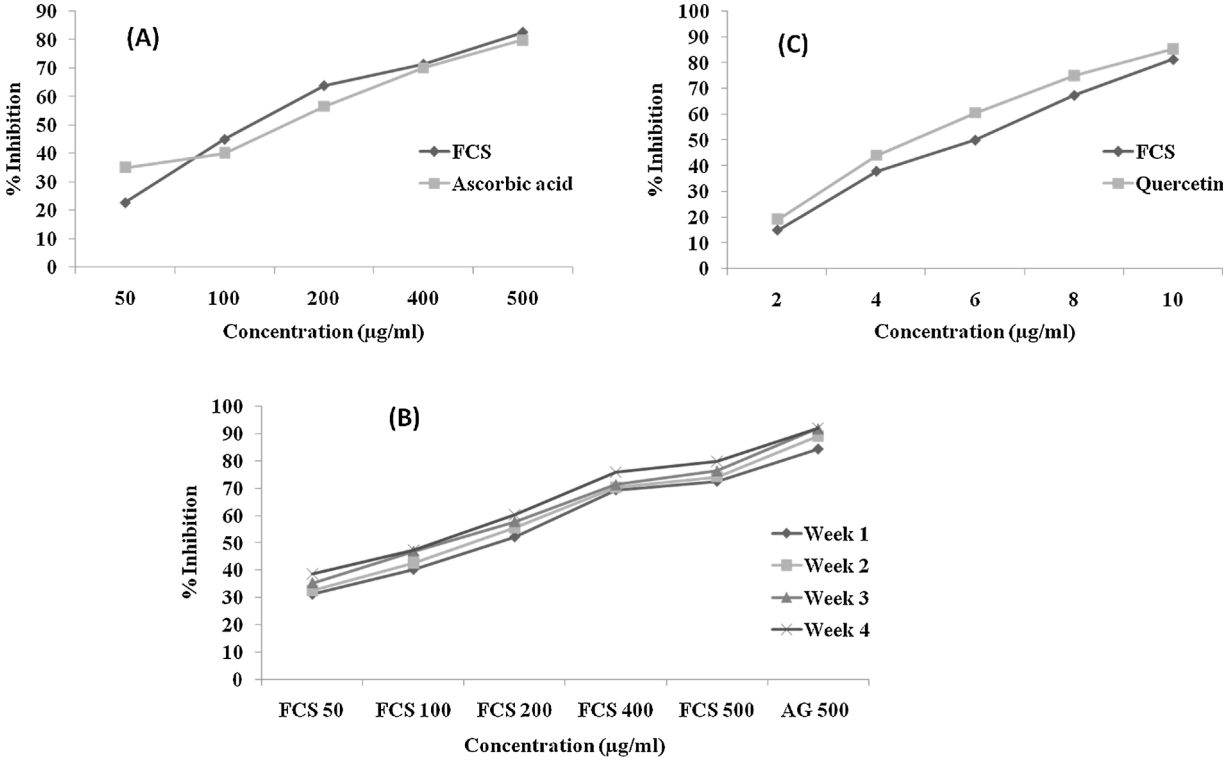

Fig. 4. Inhibitory effects of FCS against A: Sorbitol accumulation, B: AGEs inhibition and C: ALR enzyme inhibition.

confirmed the presence of the hydroxyl groups, ketones, alkanes and alkenes.

3.2. Inhibition of aldose reductase enzyme

ALR is a NADPH dependent cytosolic oxidoreductase enzyme responsible for the reduction of aldehydes and carbonyls including monosaccharides. ALR tends to have low affinity for glucose therefore no major effects on glucose metabolism is observed under normal physiological conditions [4,5]. Due to chronic hyperglycemia, hexokinase enzyme (responsible for phosphorylation of glucose for energy production) gets saturated and excess of glucose enters to another pathways like polyol pathway and a consequent rush in the rate of polyol pathway augments the reduction of various glucose to sorbitol. ALR utilizes cofactor (NADPH) for reduction of glucose to sorbitol under hyperglycemic conditions. The over-utilization of NADPH by ALR enzyme simultaneously affects other homeostatic mechanisms including reduction in glutathione (GSH) production; an antioxidant enzyme, ultimately contributes to increased oxidative stress [4,8]. In our experiments, we have obtained the enzyme ALR from kidney of Wistar rat and the activity of ALR was measured spectrophotometrically by monitoring the oxidation of NADPH at 340 nm. FCS has produced good inhibitory effect against ALR enzyme with IC_{50} 6.08 µg/ml in comparison to quercetin (standard) *i.e.* 6.69 µg/ml. ALR inhibitory effects may be an additive effect of different flavonoids present in FCS (Fig. 4). Shimizu et al. [15]; Jung et al. [5]; Ghamali et al. [16]; Patil and Gacche [17] have also studied the active potential of flavonoids against ALR enzyme which supports our results.

Table 2
Binding interactions of ALR, RAGE and sorbitol dehydrogenase with identified constituents of FCS.

Targets	Compound	Docking score	Hydrogen bonding		Hydrophobic interaction
			Amino acid	Distance (Å)	
ALR	(F_1)	−2.65	SER_{218}	2.52	–
	(F_2)	−3.33	TYR_{209}	2.12	TRP_{111}, CYS_{298}, ILE_{260}
			ASN_{160}	2.43	
	(F_3)	−3.22	TRP_{319}	1.64	–
	(F_4)	−2.94	–	–	SER_{214},TRP_{20A}, LYS_{21A}, ILE_{260}
	(F_5)	−3.52	TRP_{219}	1.75	–
	(F_6)	−2.78	TRP_{219}	1.57	GLN_{183}, ILE_{260}, ASP_{43A}, LYS_{77A}, TYR_{209}
	(F_7)	−3.46	SER_{214}	2.14	–
RAGEs	(F_1)	−3.11	Van der waal's interactions only		
	(F_2)	−1.34	–	–	GLY_{199}, VAL_{229}, THR_{195}, LEU_{332}, VAL_{194}
	(F_3)	−2.61	Van der waal's interactions only		
	(F_4)	−2.17	–	–	ASP_{201}, PRO_{196}, GLY_{200}, VAL_{229}, PRO_{132}
	(F_5)	−3.03	Van der waal's interactions only		
	(F_6)	−0.52	–	–	THR_{134}, PRO_{196}, LEU_{133}, VAL_{229},GLU_{132}
	(F_7)	−3.01	Van der waal's interactions only		
	AG (standard)	−2.21	GLY_{45B},	1.23	ASP_{201}, PRO_{196}, GLY_{200}, VAL_{229}, PRO_{132}
Sorbitol dehydrogenase	(F_1)	−4.78	Van der waal's interactions only		
	(F_2)	−4.94	–	–	CYS_{44B}, GLY_{453}, ILE_{56B}, LEU_{274}, SER_{46B},GLY_{672}
	(F_3)	−3.84	Van der waal's interactions only		
	(F_4)	−4.39	–	–	ILE_{183},PRO_{182},GLY_{45B}, CYS_{44A}
	(F_5)	−4.84	Van der waal's interactions only		
	(F_6)	−4.61	–	–	PRO_{182}
	(F_7)	−4.75	Van der waal's interactions only		
	Ascorbic acid	−3.98	Van der waal's interactions only		

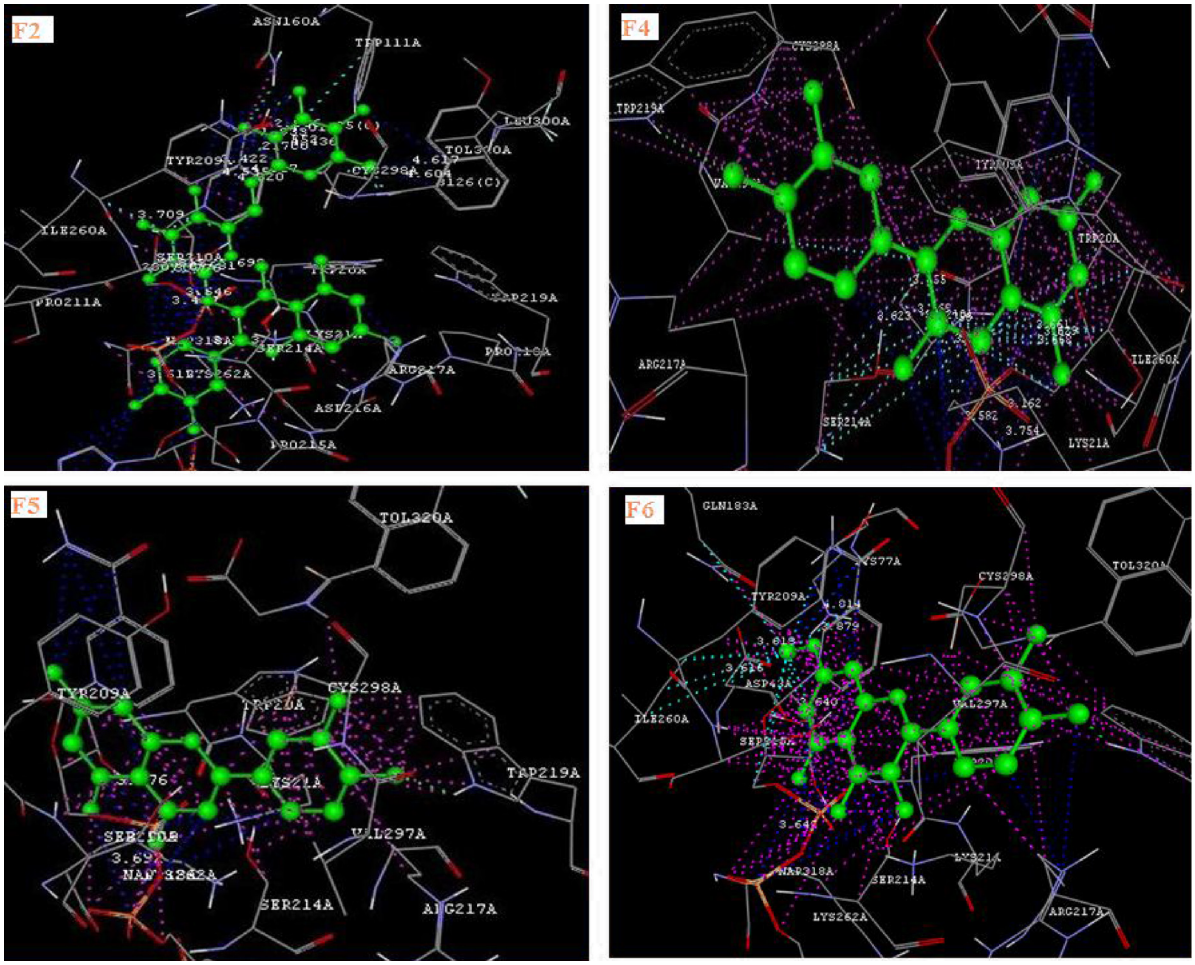

Fig. 5. Binding interactions of F_2, F_4, F_5 and F_6 with ALR enzyme.

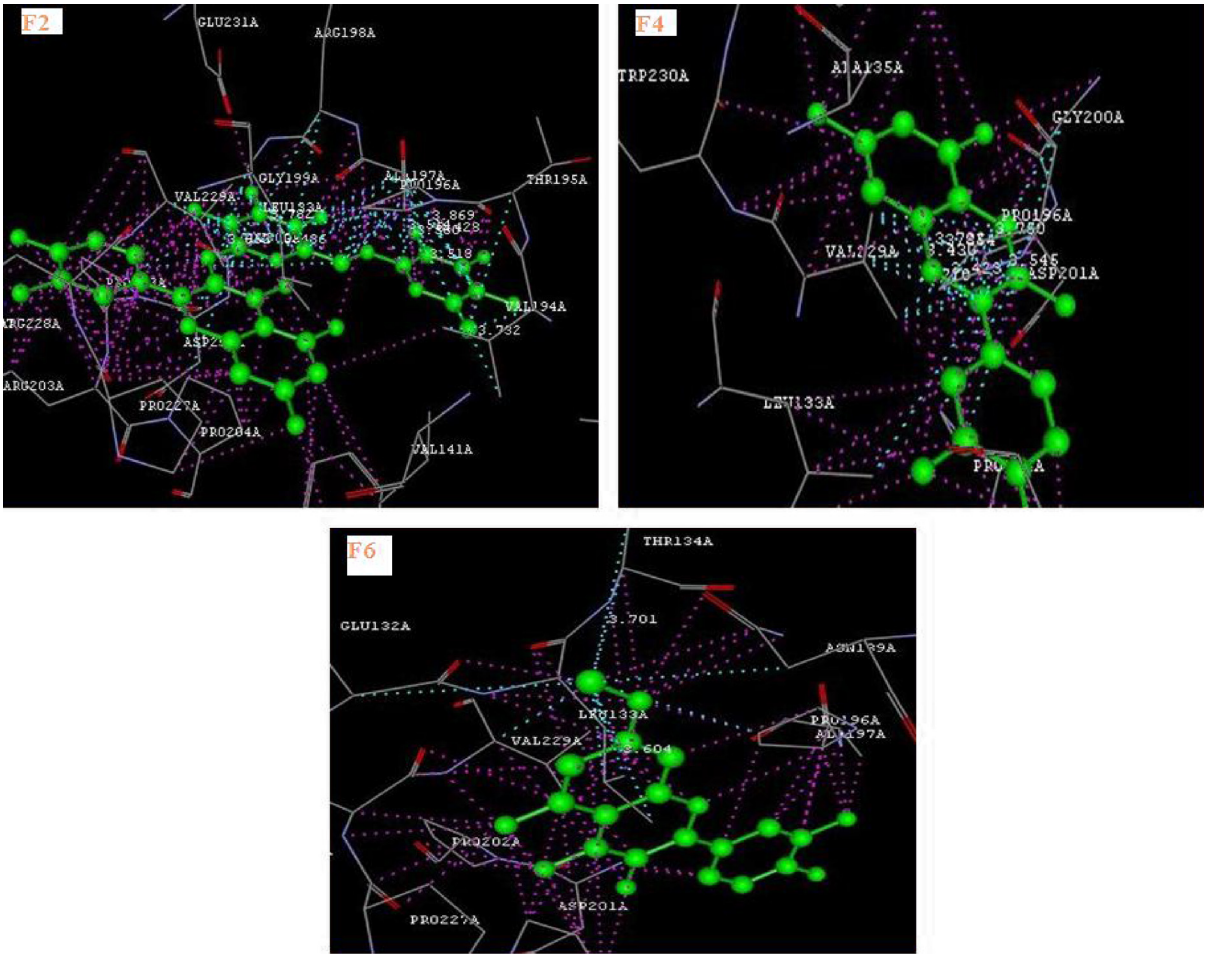

Fig. 6. Binding interactions of F_2, F_4, and F_6 with RAGEs.

3.3. Inhibition of AGEs

During the course of diabetes, chronic hyperglycemia also leads to non enzymatic glycation which results to formation of amadori products (formed by a reaction between reducing sugars and proteins/lipids) by Maillard rection. Amadori products are further converted to cross-linking AGEs, including pentosidine and crosslines, which have characteristic fluorescence. Excessive formation of AGEs also over expresses the receptor of AGEs known as RAGEs and collectively contributes to pathogenesis of diabetic complications. Various studies confirmed that inhibition of AGEs plays a vital role in attenuation of diabetic complications [8,20,29,30], therefore, AGEs inhibition could be considered as a good therapeutic approach that may alter pathogenesis and delay the progression of diabetic complications. In our present study, the formation of AGEs was monitored weekly by measuring fluorescence intensity of the bovine serum albumin (BSA)-fructose solutions for subsequent four weeks and FCS was found to have inhibitory effect against formation of AGEs. After 4^{th} week of incubation, inhibition of AGEs formation by aminoguanidine (standard, 500 µg/ml) was 92.54% whereas FCS (500 µg/ml) inhibited 79.80% of AGEs (Fig. 4).

3.4. Erythrocyte sorbitol accumulation inhibition

Sorbitol (alcoholic sugar); obtained by glucose reduction using ALR enzyme and metabolized at a very slow rate and produces laxative effect by drawing water to the large intestine. Sorbitol and its metabolites accumulate in proportion to the extracellular concentration of glucose in sensitive tissues like eye lens, retina, renal cells, peripheral nerves etc. and inefficient metabolism, resulting in the development of long term diabetic complications including nephropathy, neuropathy, retinopathy etc [4,7]. In our present study, we have prepared different concentrations of FCS and measured their effect against sorbitol accumulation in terms of relative fluorescence due to NADH. Different concentrations of FCS were found to exhibit significant inhibitory effect on accumulation of sorbitol in red blood cells with an IC_{50} 221.0 µg/ml which was comparable to Ascorbic acid *i.e.* 183.08 µg/ml (Fig. 4).

3.5. Molecular docking study

Docking study is a computa tional method used to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search. In our present study, we have targeted three binding site for ALR, RAGEs and sorbitol dehydrogenase by using identified constituents of FCS. The constituents F_2, F_4 and F_6 have shown good binding interactions with all the receptors. All the constituents except F_4 were found to have hydrogen bonding and hydrophobic interactions with receptor site of ALR enzyme. The results are given in Table 2 and Figs. 5, 6 and 7 .

4. Conclusion

This study has demonstrated the inhibitory potential of FCS against formation of AGEs, accumulation of sorbitol and activation of ALR enzyme. These inhibitory activities may be a possible contribution of phytoconstituents like flavonoids present in FCS. This aspect is

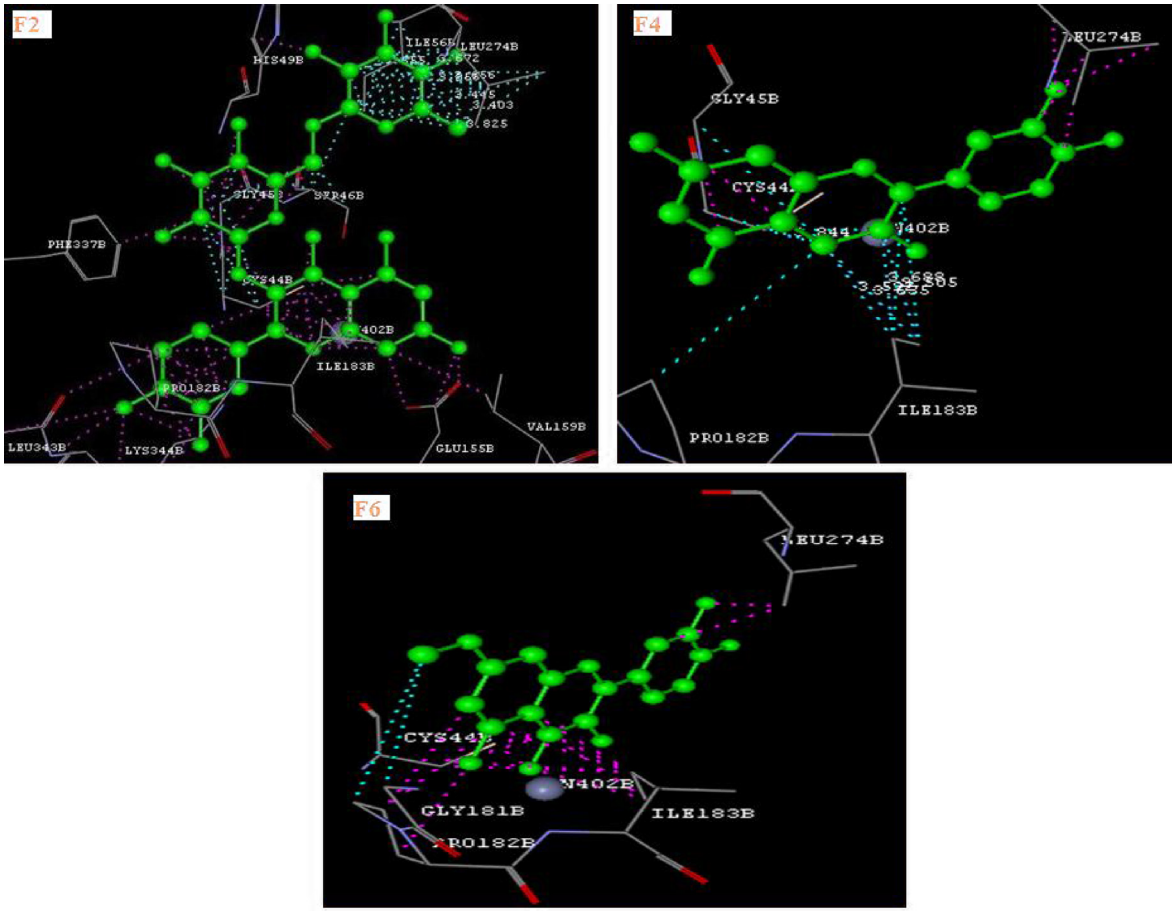

Fig. 7. Binding interactions of F_2, F_4 and F_6 with Sorbitol dehydrogenase.

supported by molecular docking studies, in which the identified constituents have shown good binding interactions with all the receptor sites especially with ALR enzyme. Thus, FCS may have beneficial role in attenuation of diabetic complications and needs to be explored for *in vivo* inhibitory potential against diabetic complications. Furthermore, the targeted sites could be used for development and screening of new agents against pathogenic markers of diabetic complications.

Conflict of interest

The author has no conflict of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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