Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/17118
DOI URL: http://dx.doi.org/10.21474/IJAR01/17118

RESEARCH ARTICLE

IN-VITRO ANTIDIABETIC ACTIVITY OF SWIETENIA MAHAGONI (L). SEEDS AND ITS DIFFERENT FRACTION WITH ISOLATED COMPOUNDS

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Manuscript Info

Manuscript History
Received: 20 April 2023
Final Accepted: 24 May 2023
Published: June 2023

Key words:-
Swietenia Mahagoni, α-Amylase, α-Glucosidase, Diabetes Mellitus, DRF, Inhibition Activity

Abstract

Active compounds of Swietenia mahagoni seed have power as anti diabetic that can be used in diabetes mellitus treatment. S. mahagoni seeds were extracted using methanol-maceration, followed by partitioning with petroleum ether (PE), chloroform (CL), ethyl acetate (EA), and dia-ion resin (DR). Column chromatography was used to further separate the dia-ion Resin fraction in order to get isolate purer compounds. One of the strategies is maintaining postprandial glucose level through inhibition of α-amylase and α-glucosidase. So that pre-prandial and post-prandial glucose levels can be controlled properly. The aim of this study was to determine in vitro inhibitory activity of Swietenia mahagoni seed by α-glucosidase, α-amylase. Inhibitory activity was measured using spectrophotometric method, α-amylase activity was measured at λ = 540 nm, α-glucosidase activity measured at λ = 405 nm. DRF inhibit both α-glucosidase and α-amylase better than acarbose as a positive control. This study showed that some extracts and some isolated compounds have inhibition activity of α-glucosidase and α-amylase. According to the findings, DR fraction (IC-50 = 328.22µg/mL) had a higher level of alpha-glucosidase inhibitory activity than acarbose (IC-50 = 336.95µg/mL). The six DR fractions compounds were separated using column chromatography. The DR fraction (40.62%), (50.39%), showed the highest inhibition activity.

Introduction:-

Diabetes mellitus is a different group of symptoms characterized by hyperglycemia, abnormal lipid and protein metabolism, along with specific long-term complications disturbing the retina, the kidney, and the nervous system mainly (Al-Bari, 2015). Consumption of calorie-rich diet, obesity, and lazy life style have lead to remarkable increase in the number of diabetics worldwide especially in Asia.(De et al., 2011) Diabetes mellitus (DM) is a metabolic disorder of multiple causes characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (Katakami, 2018). The effects of diabetes mellitus include long–term damage, dysfunction, and failure of various organs (American Diabetes Association, 2009). Diabetes mellitus is divided into three main types. Type-1 diabetes (insulin-dependent diabetes mellitus) is an autoimmune disorder when insulin-producing cells of the pancreas in the body have been destroyed and the pancreas produces little or no insulin(American Diabetes Association, 2009). A person who has type 1 DM must take insulin daily to live. It develops most often in children and young adults (Dorofeyeva, 1975). Type-2 diabetes has also been known as another term “insulin-independent diabetes mellitus” which accounted for

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more than 90% of diagnosed cases of DM in adults. It is a diagnosis in which the pancreas produces enough insulin but the body cannot use the insulin effectively, a condition called insulin resistance (Alam et al., 2021). Gestational diabetes mellitus (GDM) is a degree of glucose intolerance with onset or first recognition in the second or third trimester of the period of pregnancy. GDM is caused by the hormone of pregnancy or a shortage of insulin. GDM is one of the most popular disorders of metabolism during pregnancy (Mumtaz, 2000). Hyperglycemia causes damage to eyes, kidneys, nerves, heart and blood vessels (Tran et al., 2020). Diabetes prevalence estimates more than two times at 2030 from 171 million people (2000) and will be seventh leading cause of death (Mathers & Loncar, 2006). It will be global burden for low- and middle-economic countries, so diabetes was one of four targeted priorities of non-communicable diseases in the 2011 (Sukardiman & Ervina, 2020). Plants provide great alternatives to manage diabetes. It was used in many developing countries with natural diversity resources. The plants are not only hypoglycemic or insulin mimetic, but also preventing the complications; which no synthetic drug provide both properties (Ogunlana et al., 2021). Some have been shown in ß-cells regeneration function and delaying the insulin resistance, while others have antioxidant and cholesterol lowering activities (Tangvarasittichai, 2015). More than 1200 plants were found in ethno-pharmacological surveys for blood sugar lowering properties (Pandey et al., 2011). As per ancient literature, more than 800 plants are reported to have antidiabetic properties (Newman & Cragg, 2016). According to the World Health Organization (WHO), traditional medicines using plant extracts continue to provide health coverage for over 80% of the world's population. It is reported that 41% of medicine in the USA and 50% in Europe contain constituents from natural products which prove that the trend of using natural products is increased (World Health Organization, 2013). Meliaceae plants are attracting considerable interest, because of their significant biological activities. Secondary metabolites like alkaloids, flavonoids, tannins, phenolic compounds, terpenoids, glycosides that hold various pharmacological properties are due to the presence of bioactive plant compounds (Mickymaray, 2019). Biological activities of the plant are due to the abundance of phenolic compounds including different terpenoids and limonoids (Tungmunnithum et al., 2018). The chemical entities of this plant have been proved for their anti-bacterial, anti-fungal, anti-malarial, anti-oxidant , anti-ulcer, anti-viral, antidiarrhoeal, anti-pyretic and anti-inflammatory properties (Waziiroh et al., 2018). Considering the above evidence, the study was planned to identify the Phytocompounds of the Swietenia mahagoni (L.) Jacq. seed responsible for their biological property.

S. mahagoni belongs to the family of Meliaceae; it is also called as West Indian Mahogany. It is extensively used as medicine for several diseases and widely grown plant of Bangladesh. S. mahagany is a large, deciduous and economically important timber tree; it is mainly cultivated in the tropical zone, such as India, Malaysia and Southern China. Mahogany can reach 75 feet in height, leaves are evergreen or semi-evergreen, flowers are unisexual, and the tree is monoecious (Sahgal et al., 2009).

Materials And Methods:-

Plant materials

The plant S.mahagoni (Mahagoni) seeds was selected for the Chemical and Biological investigations. The whole seeds were collected from 'Gurudaspure' in Nator district, Bangladesh, in March, 2021. The collected plants materials were shade dried for several days. The dried plant materials were ground into coarse powder by a grinding machine, (Model: FFC DISK MILLS, JIMO QINGDAO RXCO PRECISION MACHINERY CO. LTD. CHINA) in the Organic Research Laboratory department of Chemistry, University of Rajshahi, Rajshahi.

The extracts were prepared from five solvents according to its polarity from low to high. The solvents used for the extraction are petroleum ether, chloroform, ethyl acetate, methanol and water. The samples are filtered using Whatman no. 1 filter paper and the filtrates were used for further analysis.

Procedure of Extraction:

Dried plant of S. mahagoni seeds were carefully extracted with methanol (MeOH, Analytical Grade, BDH Laboratory Supplies) in maturation system. The resulting juicy extract was filtered through Whatman paper No.1 and concentrated under reduced pressure at 40°C using the Buchi Rotavapor R-200 to obtain a crude residue (25.5%).The process have done for several time to increase the crude extract. After evaporation of the methanol solvent, the extracted was passed through a previously well packed dia-ion resin column which has selectivity to collect only the phenolic group compounds. Then the materials, which were bound in resin column, were collected by passing methanol solvent. Another portion of the crude methanol extract (CME) was triturated with petroleum ether, chloroform and ethyl acetate respectively. Finally petroleum ether, chloroform and ethyl acetate triturate were collected and evaporated.

Phytochemical Results:

Table 1:- Phytochemical screening of crude methanol and its four fractions of S. mahagoni seeds.

Phytochemical constituents	Crude Methanol extract	Petroleum ether fraction	Chloroform fraction	Ethyl acetate fraction	Dia-ion Resin fraction
Saponins	+ +	+ +	+	+ +	++ +
Tannins	+	−	−	−	+ + +
Glycosides	++	+	+	++	+ +
Steroids	+ +	+ +	+	+ +	++ +
Alkaloids	+ + +	−	+ +	+	+ + +

Here, + = Present in the mild amount, + + = Present in the moderate amount, + + + = Present in the large amount, − = Not present.

Results obtained for qualitative screening of phytochemical components in the different extract on different solvent extracts of S. mahagoni seeds are presented in Table.

Fractionation of the Dia-ion Resin fraction (DRF) by column chromatography:

A total of 226 fractions were obtained from the column chromatography of the dia-ion resin fraction (DRF) after eluting with the different ratio of solvent-solvent system as mentioned in the table 2. Each of the fractions was checked by TLC plates developed with the solvent system petroleum ether: acetone as mobile phase and viewed visually, under UV, I_2 chamber and with vanillin-sulphuric acid spray reagent.

The fractions of the similar behaviors were combined and the fractions were designated as F-1 to F-20 respectively. Table-2 is a list of observation following TLC examination of the fractions obtained from column chromatography of the (DRF).

Table-2:- Solvent system used in the column analysis of dia-ion resin fraction.

Collection no.	Fraction no.	Solvent systems	Proportion	Volume eluted (ml)
1 to 12	F-1	Petroleum Ether	100%	300
13 to 19	F-2	Pet .ether : Acetone	95 : 5	300
20 to 32	F-3	Pet. ether : Acetone	90 : 10	350
33 to 41	F-4	Pet. ether : Acetone	85 : 15	350
42 to 54	F-5	Pet. ether : Acetone	80 : 20	350
55 to 68	F-6	Pet. ether : Acetone	75 : 25	350
69 to 72	F-7	Pet. ether : Acetone	70 : 30	350
73 to 84	F-8	Pet. ether : Acetone	65 : 35	300
85 to 97	F-9	Pet. ether : Acetone	60 : 40	300
98 to 112	F-10	Pet. ether : Acetone	55 : 45	350
113 to 124	F-11	Pet. ether : Acetone	50 : 50	350
125 to 137	F-12	Pet. ether : Acetone	45 : 55	350
138 to 149	F-13	Pet. ether : Acetone	40 : 60	350
150 to 161	F-14	Pet. ether : Acetone	35 : 65	350
162 to 175	F-15	Pet. ether : Acetone	25 : 75	300
176 to 185	F-16	Pet. ether : Acetone	15 : 85	300
186 to 192	F-17	Pet. ether : Acetone	5 : 95	300
193 to 207	F-18	Acetone	100%	300
208 to 213	F-19	Methanol: Acetone	25 : 75	300
214 to 226	F-20	Methanol: Acetone	50 : 50	300

Analysis of fraction-1 (F-1):

Analysis of F-1 showed double spots and tail on TLC using solvent system petroleum ether: acetone (5:2), R_f values 0.85, 0.82 and another two spots combined on TLC using solvent system n-hexane: ethyl acetate: methanol (5:2:0.5) with R_f values 0.65, 0.61. The spots were viewed under UV and iodine chamber. These spots showed positive test (dark pink color) with vanillin-sulfuric acid spray reagent. But for the poor amount of this sample (8.76 mg), this fraction was not further analyzed using PTLC for the purification.

Analysis of fraction-2 (F-2):
Analysis of F-2 showed double spots on TLC using solvent system petroleum ether: acetone (5:3), R_f values 0.85, 0.80 and another single spot on TLC using solvent system n-hexane: ethyl acetate: methanol (5:1:0.5) with R_f values 0.60. The spots were viewed under UV and iodine chamber. These spots showed positive test (dark pink color) with vanillin-sulfuric acid spray reagent. The amount of this sample (37.42 mg); this fraction was further analyzed using PTLC for the purification using solvent system Pet. ether: acetone (5:3). A single compound was collect by PTLC. After a few days a solid mass was obtained with slight impurities. The compound washed with acetone and filtered through cotton plugs and was collected in a beaker. The solvent was evaporated off under reduced pressure to afford the pure compound DFC-1 (27.32 mg) as solid mass. The isolated compound chemical and biological analysis had been done.

Anti-diabetic activity measurement
Anti-diabetic activity of different extracts of Swietenia mahagoni seeds was determined employing the method as described by Jabir K. V. et al., (2014).

The content of antidiabetic activity in different extractives of plant extract was determined by the well-known amylase enzyme inhibition method. In this method alpha amylase, alpha glucosidase enzyme and Acarbose were used as standard. Absorbance was measured at 540nm and 405 nm respectively.

Reagents and Instruments
Alpha amylase (Sigma Aldrich, Germany), Alpha glucosidase (α-glucosidase 0.15 U mLG1) (Sigma Aldrich, Singapore), Potassium dihydrogenphosphate 2M pH 6.8 (Merck), Substrate 4-Nitrophenyl-alpha-Dglucopyranoside(PNPG) 5mM (Sigma Aldrich, Singapore), Sodium carbonate (Merck), Acarbose (Sigma Aldrich, Singapore), soluble Starch (Sigma Aldrich, Germany) ,Sodium phosphate buffer (pH6.9), 3,5-dinitrosalicylic acid, Sodium potassium tartrate (Merck), standard of maltose 0.2%, Micropipette (10-100 µL) (BIOHIT Proline, Made in Finland), Incubator (HYSC,DI-81, Korea), UV-spectrophotometer (APEL,PD-303S, Japan).

Experimental procedure for α-amylase activity assay:
500 µL of plant extract and standard of different concentration (50, 100, 200, 500 µg/mL) solution was taken in a test tube. 500 µL of alpha amylase enzyme was added into the test tube. The test tube was then incubated at 37^0C for 10 minutes to complete the reaction. 500 µL of a 1% starch solution was added into the test tube. Again it was incubated at 37^0C for 15 minutes. 1ml of 3,5-dinitrosalicylic acid was then added into the test tube. The test tube was then incubated in boiling water bath for 5 minutes and cooled to room temperature.

Finally the reaction mixture was then diluted after adding 10ml distilled water and absorbance was measured at 540nm (Striegel et al., 2015).

Experimental procedure for α-glucosidase activity assay:
A 36 µL of phosphate buffer solution, 30 mL sample solution with various concentrations (10, 25, 50, 100 and 150 µg mLG1),17 µL PNPG substrate at concentration of 5 mM were put in 96 well microplate. This mixture was incubated at 37°C for 5 min. After 5 min, 17 µL of α-glucosidase solution, 0.15 U mLG1 was added in each well to obtain total volume of 100 mL. The mixture was incubated for 15 min to get the complete hydrolysis reaction. 100 µL of Sodium Carbonate (Na_2CO_3) 200 mM solution was then added. Absorbance was measured at 405 nm using a microplate reader. Each test was repeated twice (Ris et al., 1975).

The percentage (%) of inhibition was calculated from the following equation.
% inhibitory activity = $(A_1\text{-}A_2)/A_1 \times 100$
Where, A1: Blank abs (B*) - control of blank abs (KB**)
A2: Sample abs (S) - control of sample abs (KS***)

An experiment was performed using 5 variation of sample concentration. Percent inhibition obtained for each sample was processed in form of graph and compared to the percent inhibition of acarbose as a positive control.

Calculation of IC50:
The $\mathbf{IC_{50}}$was calculated using linear regression equation in which the concentration of the sample as the x-axis and percent inhibition as the y-axis

From the equation y = a+bx,

Result and Discussion:-

Table 3:- Data for IC_{50} values of Alpha amylase test of different fractions of Swietenia mahagoni seeds.

Name of the sample	Conc. (µg/mL)	% of inhibition Mean ± STD	IC_{50}(µg/mL)
Acarbose	250	41.32±0.04	331.40
CME	250	38.99±0.43	416.51
PEF	250	37.80±0.53	518.55
CLF	250	38.99±0.55	417.47
EAF	250	39.60±0.36	437.19
DRF	250	40.20±0.05	404.81
COM-1	250	41.26±0.23	337.62
COM -2	250	38.13±0.33	460.70

IC_{50} values of **Alpha amylase**

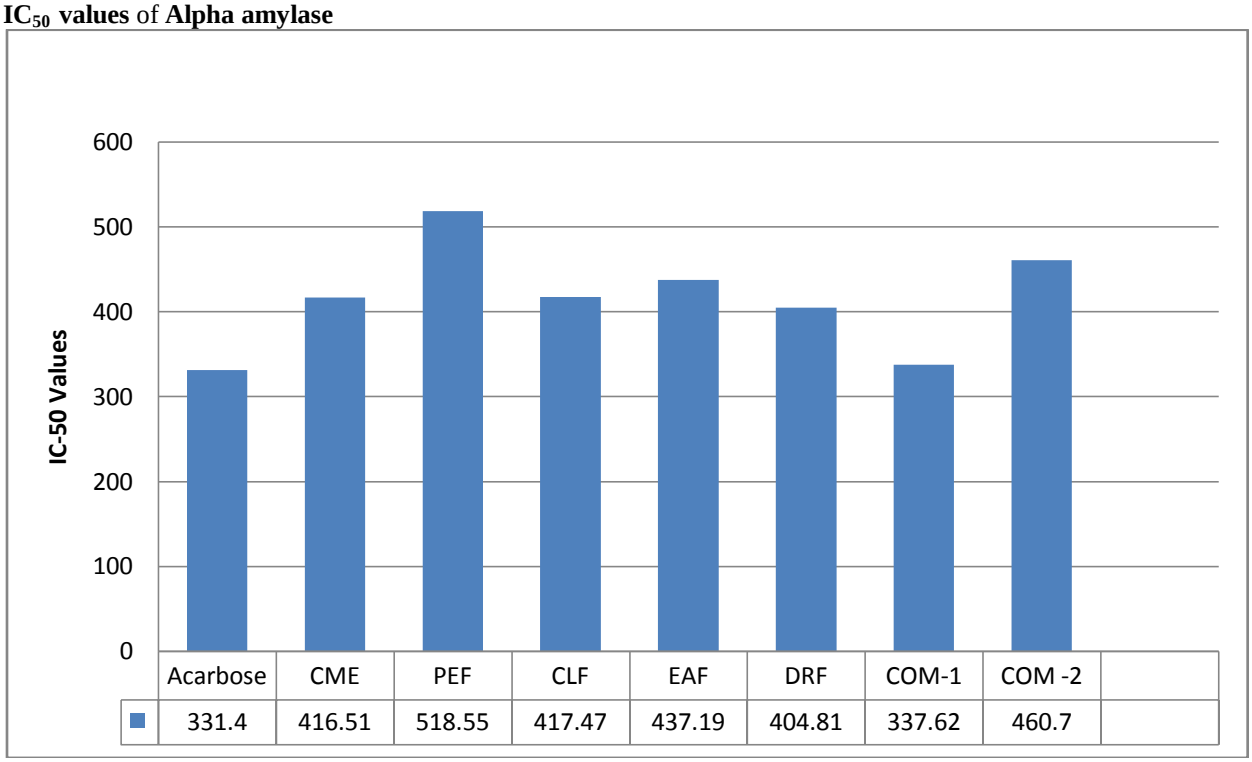
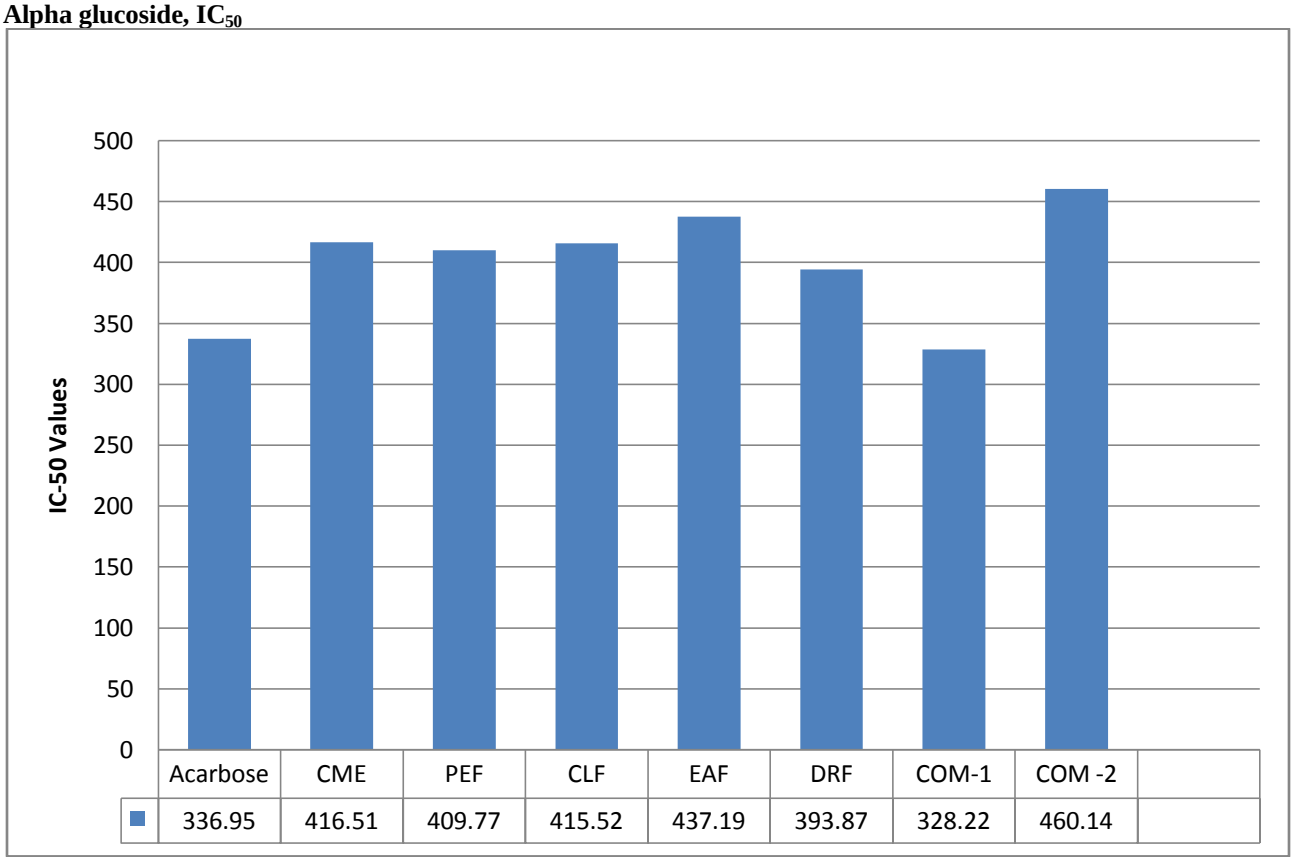


Table 4:- Data for IC_{50} values of Alpha glucoside test of different fractions of Swietenia mahagoni seeds.

Name of the sample	Conc. (µg/mL)	% of inhibition Mean ± STD	IC_{50}(µg/mL)
Acarbose	250	28.44±0.525	336.95
CME	250	39.05±0.640	416.51
PEF	250	38.78±0.531	417.38
CLF	250	38.82±0.499	415.52
EAF	250	38.59±0.366	437.19
DRF	250	40.96±0.35	393.87
COM-1	250	42.26±0.23	328.22
COM -2	250	38.47±0.06	460.14

Alpha glucoside, IC_{50}

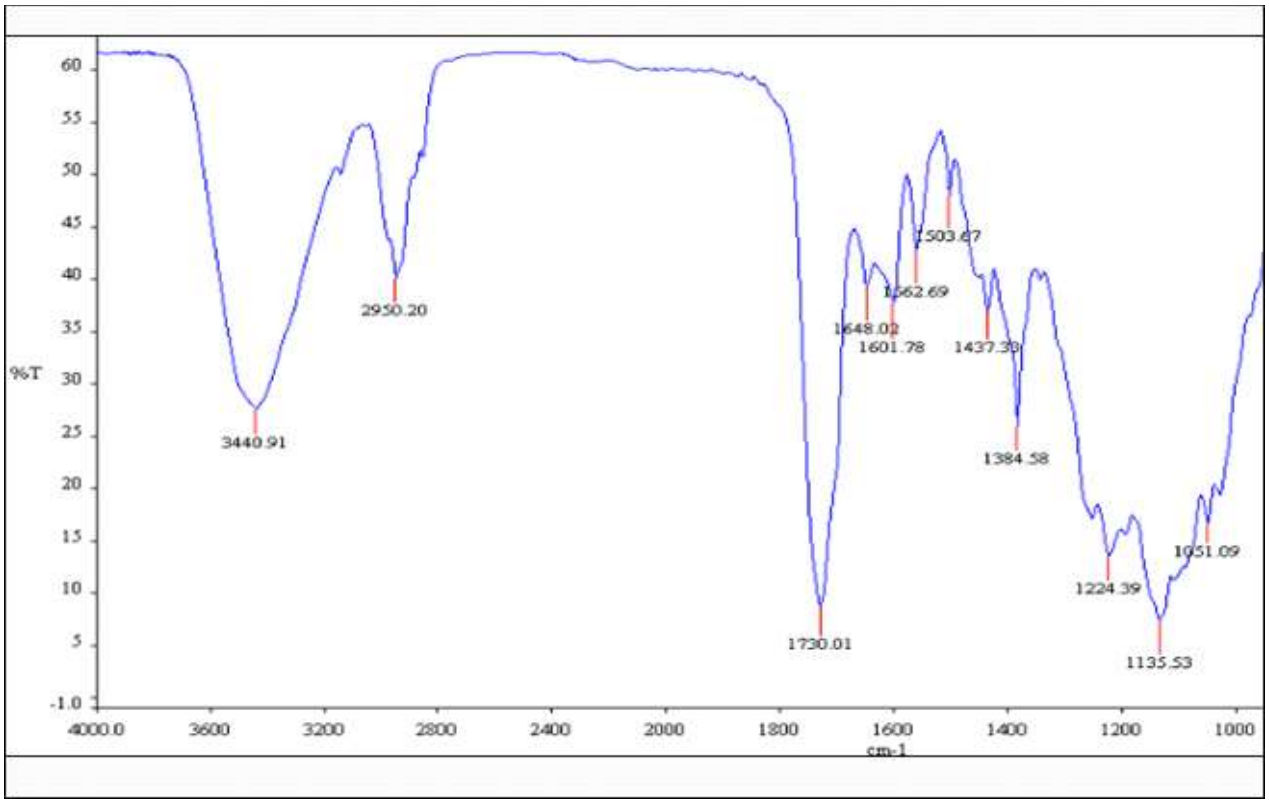


In vitro α-glucosidase inhibitory studies demonstrated that all samples had inhibitory activity (Table 4). The percentage inhibition at 20, 50, 100, 250 and 500µg /mL concentrations of samples showed a concentration dependent on percentage inhibition. The highest inhibitory activity, IC_{50} value was obtained 393.87 µg/ mL for DRF extracts, **328.22 µg/ mL for isolated compound (DRF-1)** and 336.98 µg /mL for acarbose as a positive control. It showed that inhibition activity of α-glucosidase was better than acarbose in a smaller concentration. All of them contain tannin. In recent years, tannin has been reported as non-specific inhibitors for several hydrolytic enzymes such as α-glucosidases, α-amylase (Peyrot Des Gachons & Breslin, 2016). This hypothesis can be proved by further experiments such as tannin isolation and activity assay of isolate that have been separated from other compounds. In α-amylase in vitro study, all extracts showed inhibition value between 3-99%. There were 8 samples that have inhibition values more than 80%. All of them contain glycosides. The glycosides present in the crude extracts acts as a substrate for the α-glucosidase enzyme and may be responsible for the inhibitory activity (Kato et al., 2017). Amylases degrade starch by cleaving glycosidic bonds. Glycoside was found from the sample has glycosidic bonds so it's changing the role of starch as a substrate. With this mechanism, the starch in the body was not changed to form a disaccharide. It could help the work of glucosidase which converts disaccharide into monosaccharides (glucose) and the level of glucose can be controlled. alpha glucosidase, inhibition activity of alpha amylase dependent on concentration (Peyrot Des Gachons & Breslin, 2016). Our in vitro studies demonstrated an appreciable α-glucosidase, α-amylase inhibitory activity present in 9 samples, where further experiments can be performed on animal models to confirm the hypoglycemic activity.

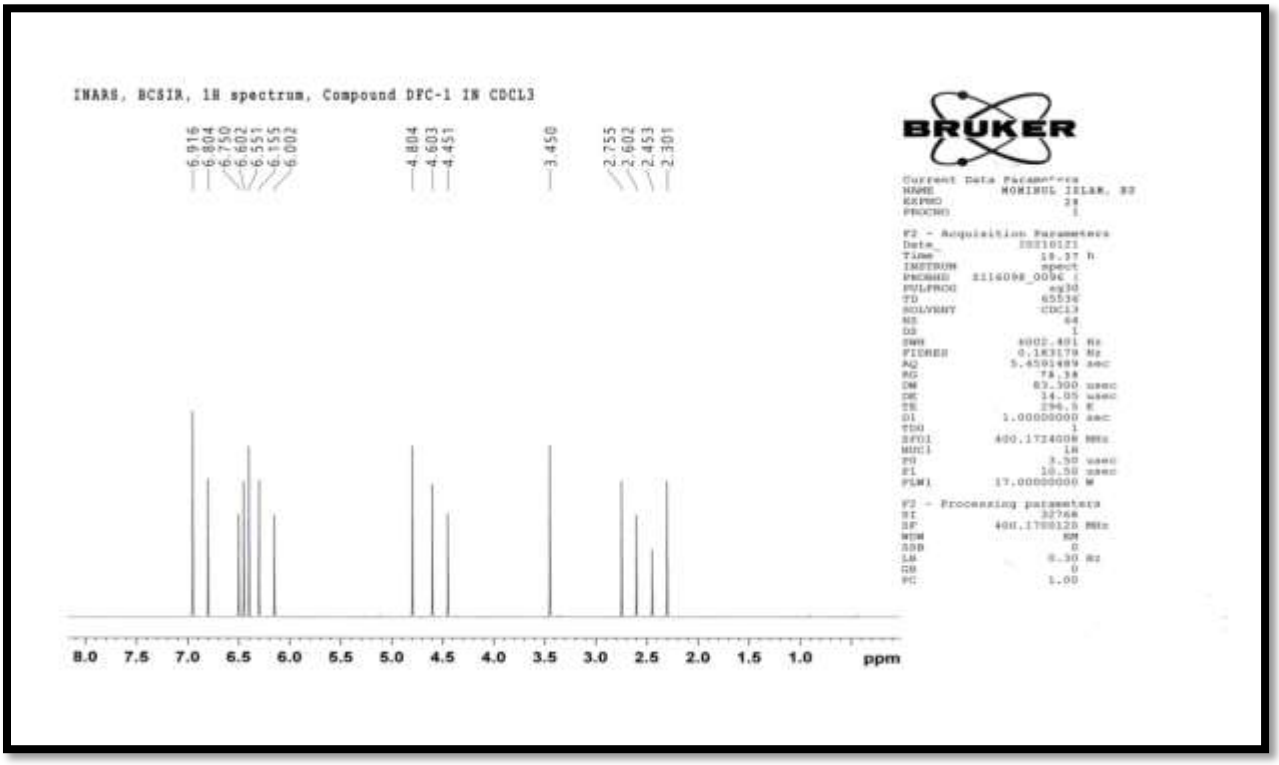
Spectroscopic data of isolated compounds DFC-1(COM-1)

UV λ_{max} (MeOH) =207, 242 and 274 nm

IR ν_{max} (KBr) = 3440 cm^{-1}(-OH), 2950 cm^{-1} (–CH_3), 1730 cm^{-1}(= CO), 1634cm^{-1}(C=C), 1434cm^{-1}(aromatic C = C) and 1135 cm^{-1} (–$COOCH_3$).

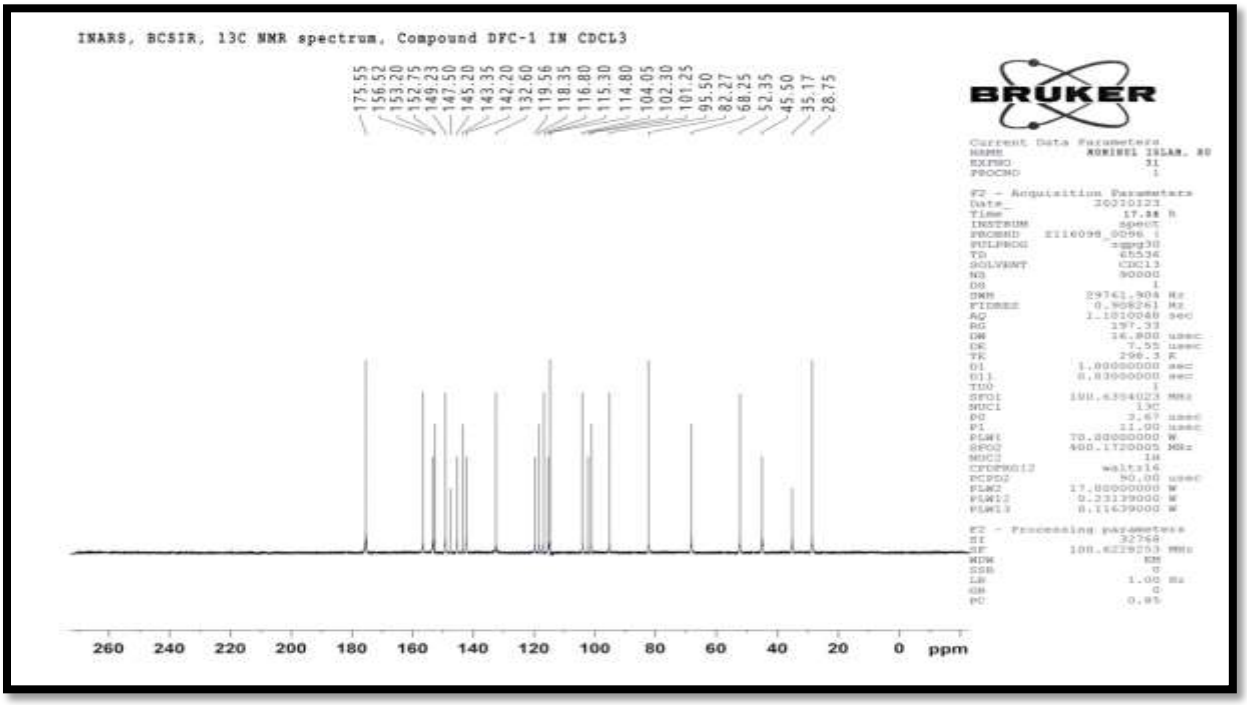


H-NMR (300 MHz) δ_{TMS} ($CDCL_3$) 2.30, 2.45, 2.60, 2.75, 3.45, 4.45, 4.60, 4.80, 6.00, 6.15, 6.55, 6.60, 6.75, 6.80, and 6.91 ppm.



^{13}C-NMR (300 MHz) δ_{TMS} ($CDCL_3$)

:28.75,35.17,45.50,52.34,68.25,82.27,95.50,101.25,102.30,104.05,114.80,115.30,118.80,118.35.119.56,132.60,142.20,143.35,145.20,147.50,149.23,152.75,153.20,156.52,and 175.55 ppm.



EI MS (m/z): 497[M]$^{+}$, 466,402,379,290, 272

Structure of new compound DFC-1

(3R)-methyl 3-(3,4-dihydroxyphenyl)-3-((3S)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4-methylchroman-8-yl)propanoate

Conclusion:-

S. mahagoni Jacq. is a commonly used herb in Folklore medicine. This paper supports all updated information on its botanical aspects, phytochemistry, pharmacological activities and traditional uses. Its chemical markers or target molecules have been identified and separated. The chemical entities of this plant have been proved for their Anti-bacterial activity, Anti-microbial activity, Anti-oxidant activity, Anti-ulcer activity, Anti-fungal activity, Anti-inflammatory, Analgesic activity, Hypoglcemic activity, Platelet Aggregation Inhibitors activity etc. These scientifically proved activities can be related with the traditional usage of the plant. Thus S. mahagoni Jacq. is one of the most important plants that has a tremendous scope for research in future. The novelty and applicability of this valuable species are hidden. Such things should be overcome through extensive scientific research. The drug may be a good candidate for developing a safe, tolerable, and promising neutraceutical treatment for the management of many diseases. Though the plant seeds are widely used for the treatment of a large number of human ailments, being an endangered species, our prime motive is to conserve such valuable plants species from going extinct.

All of the tested extracts showed inhibition activity of α-glucosidase, α-amylase for S. mahagoni seeds and have better inhibition activity of α-glucosidase than Acarbose in concentration 250 µg mL. Seeds extract which contain tannin (polyphenol) and glucoside have better inhibition activity of α-amylase in concentration 250 µg mL.

Acknowledgment:-

This work was supported byUGC of Bangladesh.

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