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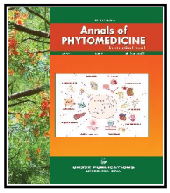

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Diabetes related enzymes inhibition, antioxidant, and hepatoprotective properties of *Pongamia pinnata* (L.) Pierre. floral methanolic extract

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Abstract

The important metabolic disorder, Diabetes mellitus (DM) and their complications poses a serious health threat to several million people and mainly related to oxidative stress. The prolonged medication causes drug toxicity and resistance. Therefore, alternative antidiabetic with antioxidant potent agent is immediately needed for DM treatment. Hence, our study investigated the antidiabetic, antioxidant and hepatoprotective properties of *Pongamia pinnata* (L.) Pierre. flower methanolic extract and found potential activities. Here, 5 mg/ml of methanolic extract of *P. pinnata* flower inhibited 66% and 72% of diabetic related enzymes α-amylase and α-glucosidase activities, respectively. Similarly, ABTS scavenging assay, DPPH free radical scavenging assay, and nitric oxide scavenging activity assays revealed the *P. pinnata* flower methanolic extracts antioxidants property and inhibited 72%, 79% and 82% of scavenging activity, respectively, after 5 mg/ml concentrations treatment. The various concentrations of *P. pinnata* flower methanolic extract hepatoprotective effect showed no toxicity towards HepG2 cells. In conclusion, based on the results, the methanolic extract of *P. pinnata* flower may use as promising alternative agent for DM treatment.

1. Introduction

Diabetes mellitus (DM) is an important metabolic irregularity which categorized by higher glucose level in the blood that can be severe or long-lasting and it may produce some general symptoms such as frequent urination, increased thirst as well as increased appetite subsequently pancreatic shortage like insulin production or a decreased cells sensitivity to insulin leads diabetic conditions and the prevalence rate of DM was estimated that 25% of world population get affected (Soumya and Srilatha, 2011; Wild *et al*., 2004; Duraisami *et al*., 2021). Commonly, the DM is controllable, but when left untreated leads severe complication including vision loss, chronic kidney disease, cardiovascular disease, neuropathy, stroke and cancer (Saedi *et al*., 2016; Arumugam *et al*., 2013). Therefore, DM is ranked sixth important cause of death due to their related complication which increases the numbers resulting serious socio-economic burden on healthcare, work loss, wages, *etc*., in developed as well as developing countries (WHO, 2016; Deshpande *et al.,* 2008). The pathogenesis of DM involved many risk factors such as metabolic irregularities, exogenesis and endogenous factors including genes and environmental behaviours (Wu *et al*., 2017). Many studies reported that, an important endogenous factoris oxidative stress which is a key factor in DM development and it is related difficulties (Prattichizzo *et al*., 2018; Rains *et al*., 2011; Calcutt *et al*., 2009; Wright *et al*., 2006). The association between diabetes and oxidative stress have been enlightened through various molecular mechanisms in which increased production of reactive oxygen species evidenced the connection to cell dysfunction and insulin resistance which causes imbalance, resulting oxidative stress which directly oxidized the proteins in diabetic process (Sanjeev and Divya, 2021; Zhang *et al.,* 2020; Folli *et al.,* 2011).Though, the antidiabetic drugs have been employed, the drug resistance and the induced drug toxicity like liver toxicity is major concern (Bennett *et al*., 2011). Therefore, to manage the DM, the cost-effective treatment option is urgently to reduce the sugar level and also, possess the antioxidant hepatoprotective property.

In the present situation, the nature always has the abundant source of significant substances that related to esteemed properties of human health (Beidokhti and Jäger, 2017; Dias *et al*., 2012). Since ancient times, several reports evidenced that the plants materials are acting as very good source for antioxidant property owing to their availability, distribution as well as plentiful biomolecules within it which has other biological properties (Xu *et al.,* 2017). The plant related biomolecules have been identified from flowers, fruits, barks, roots, stems and leaves (More *et al*., 2008; Malhotra *et al*., 2011). Therefore, *P. pinnata* from Leguminosae family is distributed most part of the world and medium sized ever green plant.The plant has several biomolecules from oils, fruits, root, leaves and barks. The *P. pinnata* has been used in Unani and Ayurveda for many years due to their antilipidoxidative, antiplasmodial, antihyperglycaemic, anti-inflammatory, antihyperammonic, antioxidant, antiulcer, and antidiarrheal properties (Sangawan *et al.,* 2010). Hence, our study investigated the *P. pinnata* antidiabetic, antioxidant, and hepato protective properties.

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2. Materials and Methods

2.1 Collection of the plant material and its authentication

The plant used in the present study was collected from a local nursery and was identified as *Pongamia pinnata* (L.) Pierre. by Dr. Mamoon AlFakhi, Chief Scientist, DM Institute of Biological Research, Omdurman, Sudan with Authentication Number DMIBR/PA/09/2024.

2.2 Methanolic crude extract preparation of *P. pinnata* flower

To prepare methanolic crude extract of *P. pinnata* flower, the fine powder of *P. pinnata* flower was purchased from local market and 20 g was added to cellulose thimble that placed in Soxhlet apparatus as cited before (Harley *et al.,* 2022). When the methanol was adding to the apparatus, the reaction started and it was run for many hours till the end product obtained. The final product used for all the studies after solvent evaporation.

2.3 α-amylase activity inhibition assay

The inhibiting ability of *P. pinnata* flower methanolic extract on α-amylase activity was investigated using α-amylase activity inhibition assay as declared earlier (Alqahtani *et al*., 2019). Briefly, the enzyme amylase and different concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) of *P. pinnata* flower methanolic extract were incubated at 25°C for 10 min, followed by adding of prepared 1% starch solution in sodium phosphate buffer (0.02 M, pH 6.9) and allowed for 15 min. Later, the above reaction mixture along with dinitrosalicyclic acid was kept for 5 min in the water bath to stop reaction and obtained resultant was read at 540 nm for α-amylase activity inhibiting percentage calculation.

2.4 Glucosidase activity inhibition assay

To determine the ability of *P. pinnata* flower methanolic extract inhibition on glucosidase activity, the glucosidase activity inhibition assay as specified before (Elya *et al*., 2008). In short, the enzyme α-glucosidase and various *P. pinnata* flower methanolic extract concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) were reacted for 10 min, followed by 5 mMp-nitrophenyl-α-D-glucopyranoside (pNPG) to the reaction mixture and again incubated for 60 min. Later, the reaction was stopped by adding 0.1 M Na_2CO_3 solution to get the end product and read at 400 nm to analyse percentage of glucosidase activity inhibition.

2.5 DPPH free radical scavenging assay

The *P. pinnata* flower methanolic extract ability to scavenge the free radicals was inspected by DPPH (2, 2-diphenyl-1-picryhydrazyl) assay as mentionedearlier (Gayathri and Sathish Kumar, 2016). Briefly, to calculate the percentage of radical scavenging activity, the mixture containing *P. pinnata* flower methanolic extract concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) and DPPH solution were allowed for 30 min interaction in a dark situation and the final end product was measured at 517 nm:

Scavenging effect = [100 × (blank OD – sample OD)]/ blank OD

2.6 ABTS scavenging assay

The scavenging ability of *P. pinnata* flower methanolic extract on ABTS (2,2'-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid) was studied using ABTS scavenging assay as cited earlier (Pacifico *et al*., 2018). Briefly, the ABTS solution (7 mM ABTS and 2.45 mM potassium persulfate ($K_2S_2O_8$) prepared was used after 16 h when the optical density reaches 0.750 ± 0.025 at 734 nm. For the assay, the *P. pinnata* flower methanolic extract concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) and diluted ABTS solution were allowed for 6 min and the attained end product was read at 734 nm for ABTS scavenging activity percentage calculation:

ABTS scavenging effect (%) = [100 x (control OD – sample OD)]/ control OD

2.7 Nitric oxide scavenging activity

The nitric oxide scavenging activity of *P. pinnata* flower methanolic extract was investigated through nitric oxide scavenging activity assay as indicated before (Alam *et al.,* 2013). Briefly, the *P. pinnata* flower methanolic extract concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) and 10 mM sodium nitroprusside prepared using 0.5 M of phosphate buffer were interacted for 60 min and Griess solution (0.1% naphthylethylenediaminedihydrochloride in 2.5% phosphoric acid) and 1% sulphanilamide in 2.5% phosphoric acid was added in equal volume to the mixture to get pink colour formation. Finally, nitric oxide scavenging activity percentage was calculated after reading the final product at 540 nm:

Scavenging activity (%) = [100 × (control OD – sample OD)]/ control OD

2.8 Hepatoprotective activity

The *P. pinnata* flower methanolic extract hepato protective property was examined on HepG2 through MTT assay as cited previously (Meiyazhagan *et al*., 2015). In short, the confluent cells in DMEM were treated with *P. pinnata* flower methanolic extract concentrations (1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, and 5 mg/ml) for 24 h followed by addition of MTT solution. The formed formazan product was dissolved using DMSO and attained product was read at 570 nm.

2.9 Statistical analysis

The error bars represented was calculated using mean and standard deviations of all the experiments.

3. Results

3.1 α-amylase activity inhibition assay

The inhibiting ability of *P. pinnata* flower methanolic extract on α-amylase activity investigated using α-amylase activity inhibition assay is presented in Figure 1. As noted in figure, the calculated percentage such as 66%, 48%, 44%, 24%, and 17% of α-amylase activity inhibition after treatment with *P. pinnata* flower methanolic extract 5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml concentrations, respectively.

3.2 Glucosidase activity inhibition assay

The ability of *P. pinnata* flower methanolic extract inhibition on glucosidase activity determined using glucosidase activity inhibition assay is represented Figure 2. As indicated in graph which displays the *P. pinnata* flower methanolic extract different concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) glucosidase activity inhibition percentage as 72%, 59%, 55%, 10%, and 5%, respectively.

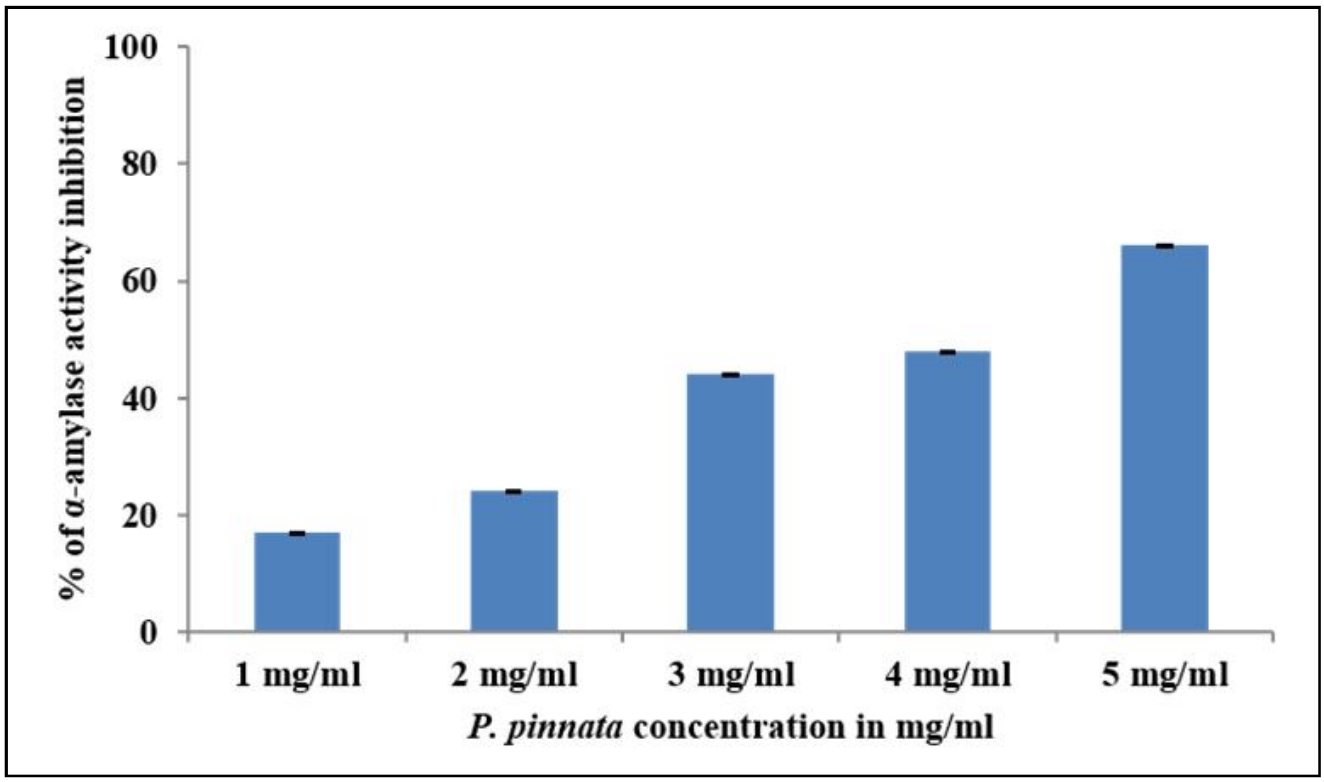

Figure 1: ***P. pinnata*** **flower methanolic extract ability to inhibit α-amylase activity.**

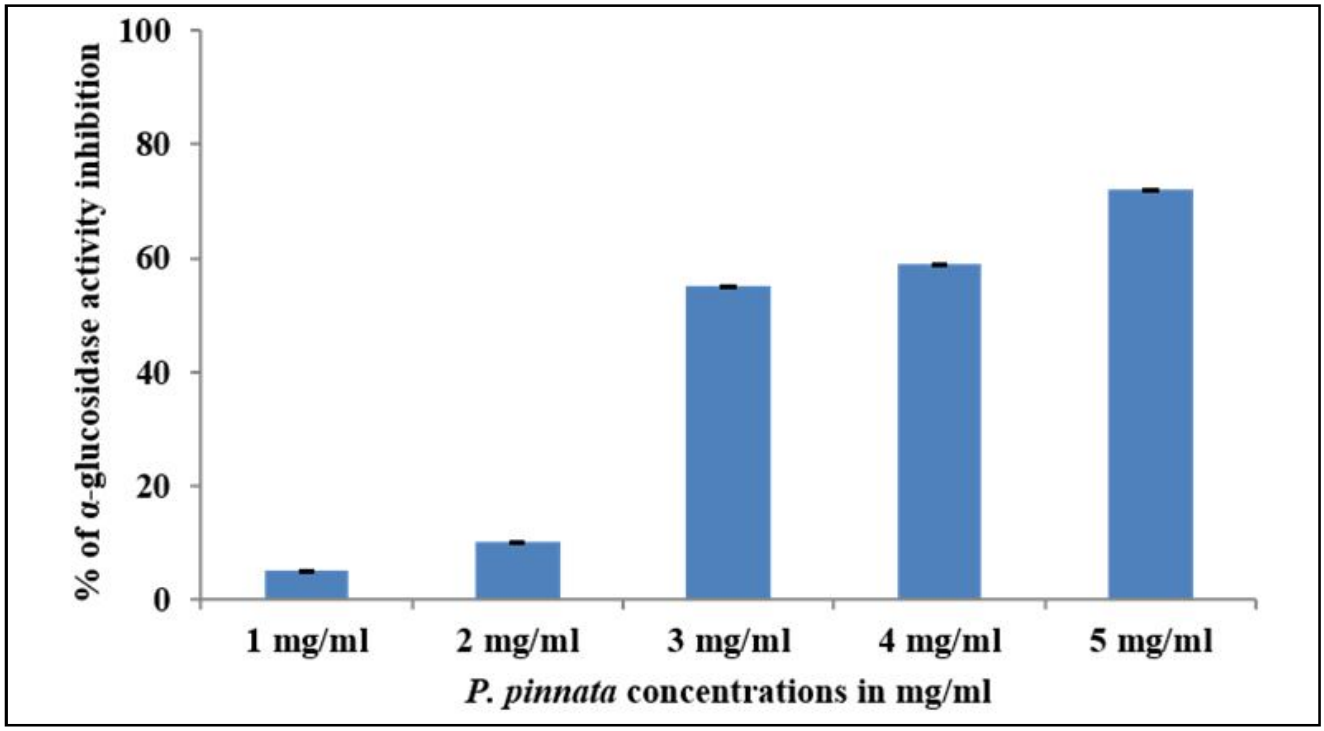

Figure 2: ***P. pinnata*** **flower methanolic extract inhibition on glucosidase activity.**

3.3 DPPH free radical scavenging assay

The *P. pinnata* flower methanolic extract ability to scavenge the free radicals inspected is presented in Figure 3. The figure exhibited the *P. pinnata* flower methanolic extract concentrations 5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml scavenging activity percentage calculated as 72%, 61%, 54%, 44%, and 35%, respectively, after treatment.

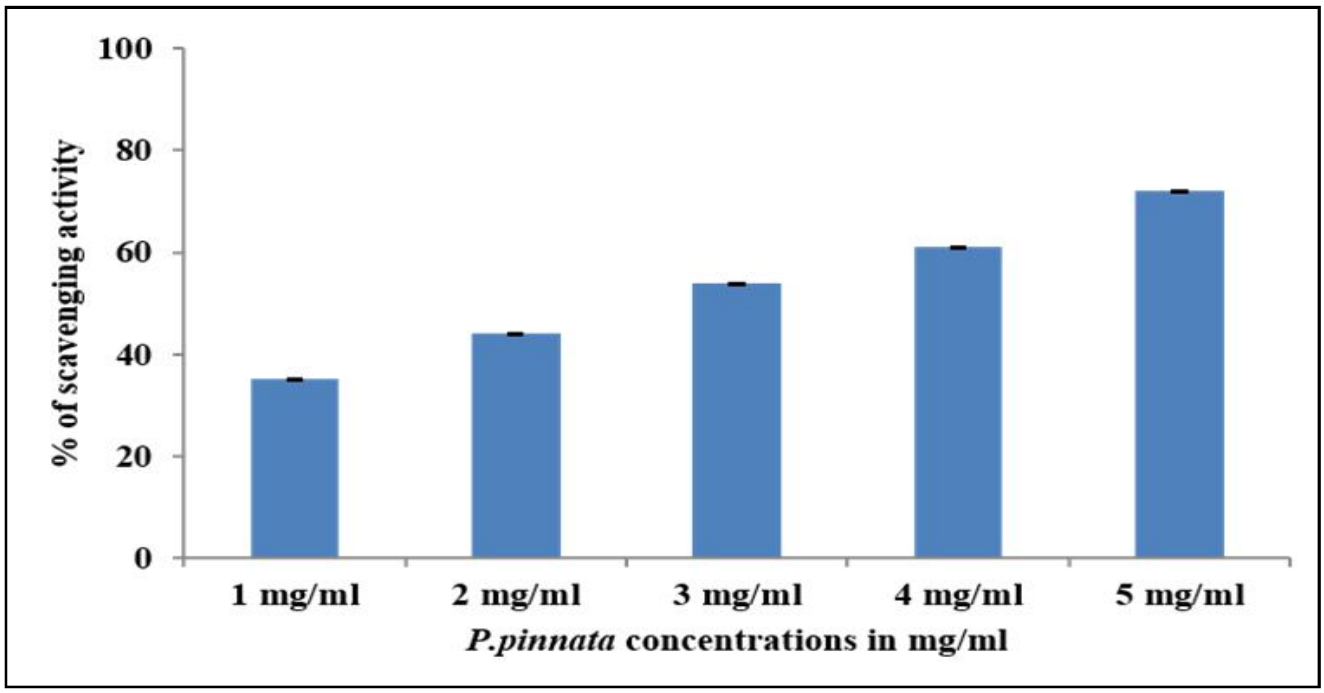

Figure 3: ***P. pinnata*** **flower methanolic extract effect on free radicals.**

3.4 ABTS scavenging assay

The scavenging ability of *P. pinnata* flower methanolic extract on ABTS (2,2'-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid) investigated through ABTS scavenging assay is mentioned in Figure 4. As observed in figure, the graph represented the different *P. pinnata* flower methanolic extract concentrations (5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml) ABTS scavenging percentage. The results revealed that, the extract showed calculated scavenging percentage as 79%, 67%, 66%, 58%, and 54%, after treatment.

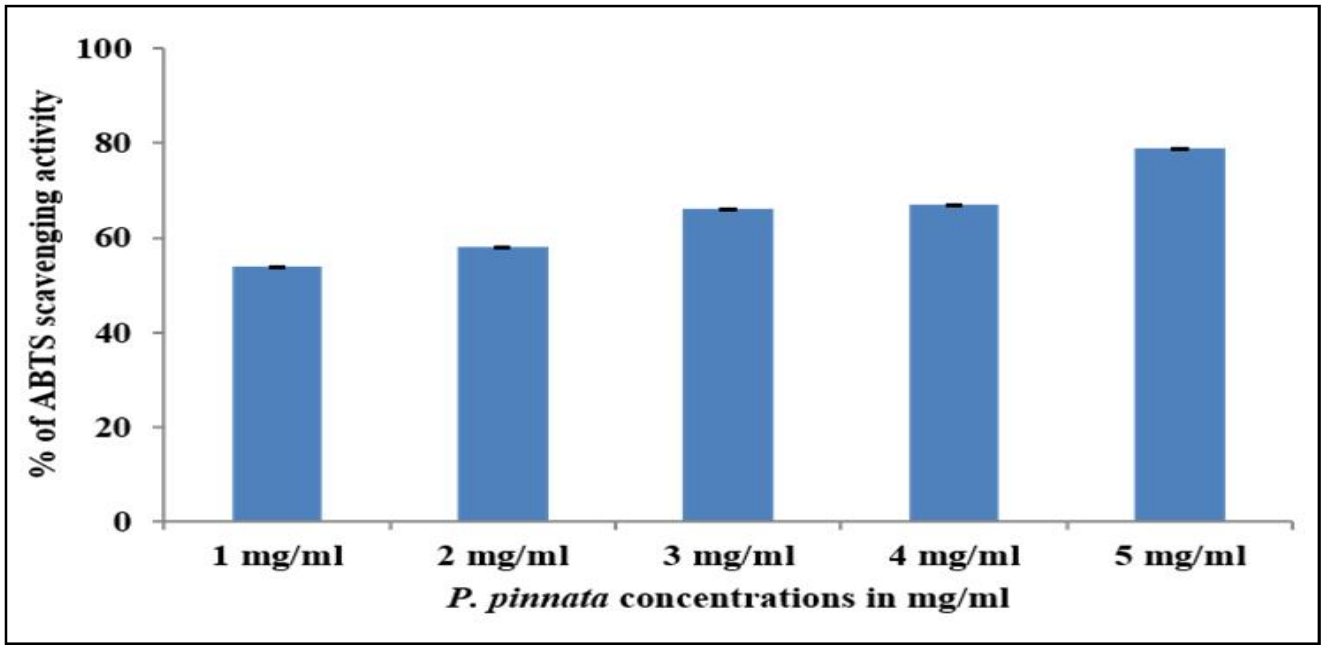

Figure 4: ***P. pinnata*** **flower methanolic extract effect on ABTS scavenging activity.**

3.5 Nitric oxide scavenging activity

The nitric oxide scavenging activity of *P. pinnata* flower methanolic extract explored through nitric oxide scavenging activity is presented in Figure 5. The figure denoted the various concentrations of *P. pinnata*flower methanolic extract nitric oxide scavenging activity percentage calculated as 42%, 58%, 64%, 73%, and 82%, after treatment.

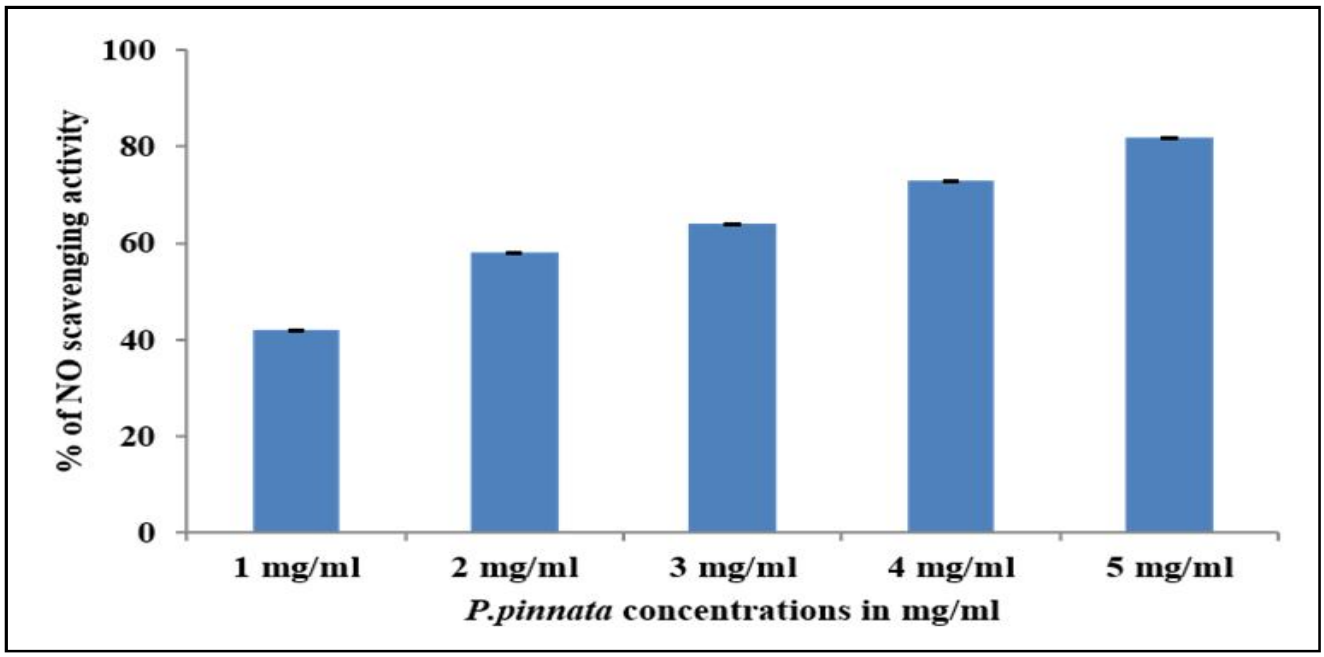

Figure 5: Nitric oxide scavenging activity of *P. pinnata* flower methanolic extract.

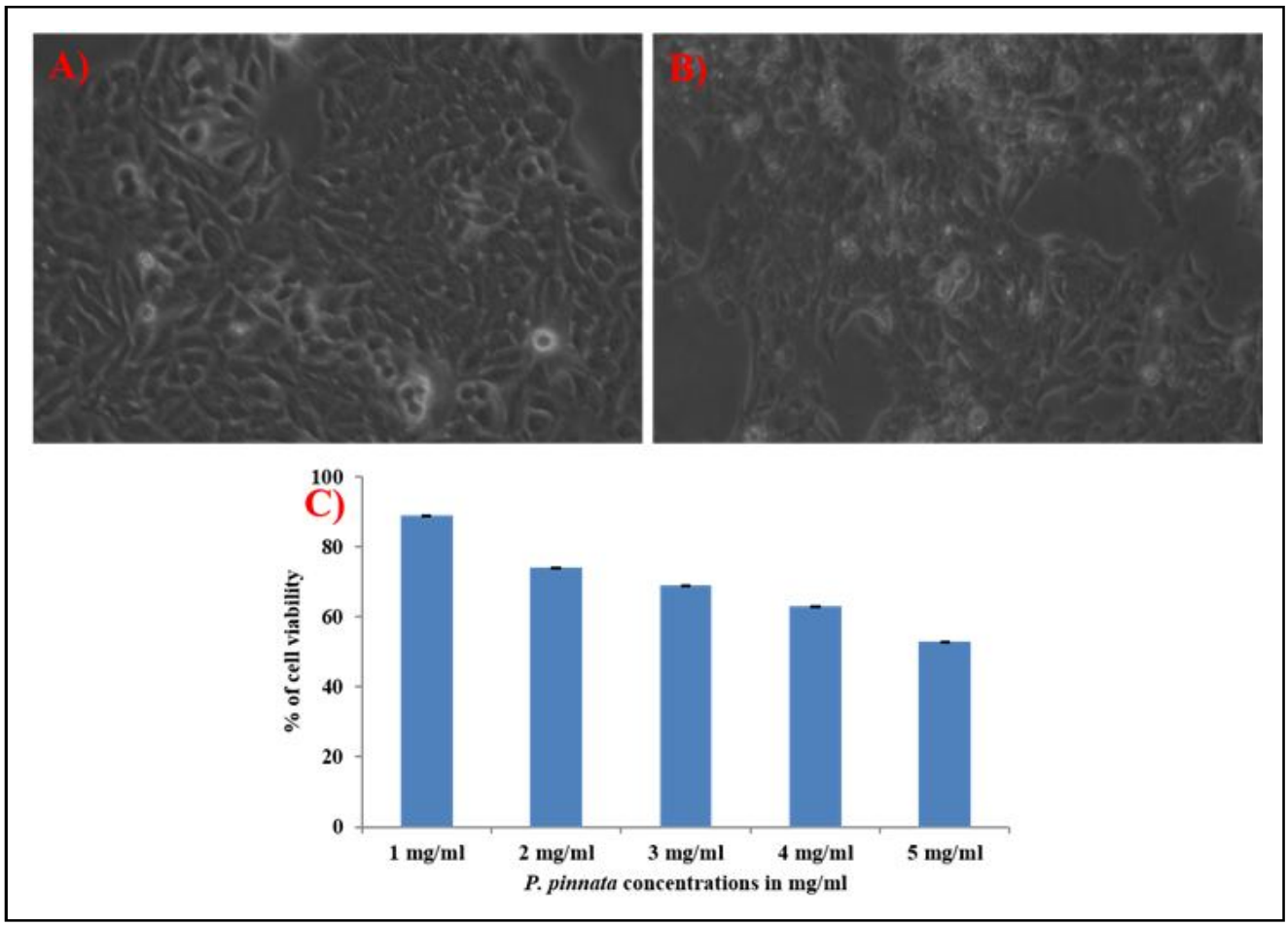

Figure 7: HepG2 cell viability percentage after different *P. pinnata* flower methanolic extract concentrations. (A) Untreated HepG2 cells, (B) HepG2 cells treated with extract, and (C) The graph dictated the cell viability percentage.

3.6 Hepatoprotective activity

The *P. pinnata* flower methanolic extract hepato protective property examined on HepG2 using MTT assay is displayed in Figure 6. The graphs denoted in figure revealed the HepG2 cell viability percentage as 89%,74%, 69%, 63%, and 53% after treating with varying 5 mg/ml, 4 mg/ml, 3 mg/ml, 2 mg/ml, and 1 mg/ml *P. pinnata* flower methanolic extract concentrations.

4. Discussion

The DM is an important chronic the metabolic disorder affecting million people that categorized by higher blood glucose level caused by various risk factors, resulting serious health issues which pose severe public threat. The side effects like liver toxicity are main drawbacks for available antidiabetic drugs. Therefore, alternative and cost-effective novel antidiabetic agents are immediately needed. Consequently, in search of novel agents, the plant related biomolecules have been identified from flowers, fruits, barks, roots, stems and leaves with potent pharmaceutical values. Hence, our study explored the *P. pinnata* flower methanolic extract antidiabetic, antioxidant, and hepatoprotective property and found promising activity. Moreover, α-glucosidase and α-amylase enzymes are chiefly played a major role in carbohydrate hydrolysis resulting glucose production and absorbed by intestine. Hence, if the both enzyme activities are stopped by novel agents leads long duration for digestion resulting decreased glucose absorption. Therefore, our study explored the *P. pinnata* flower methanolic extract antidiabetic activity by inhibiting the α-glucosidase and α-amylase activity resulting slow or decreased glucose absorption. In support of this, a study investigated the *P. pinnata* flower extract extracted using hexane was studied to determine the ability to reduce the blood glucose level in *in vivo* model of alloxan induced diabetic rats (Punitha *et al*., 2006). Similarly, another group studied the ethanolic extract of *P. pinnata* flower antihyperglycemic and antilipidperoxidative effect in normal rats as well as alloxan induced diabetic rats in which the increased lipid peroxidation, hyperglycemia, disturbed nonenzymatic condition were observed. In contrast, the *P. pinnata* flower extract administered orally in rats exhibited notable antihyperglycemic, and antilipidperoxidative effect indicted ethanolic extract of *P. pinnata* flower can be a safe alternative agent for DM treatment (Punitha and Manoharan, 2006). Sameway, other plant like *N. oppositifolia* methanolic extracted compounds, katononic acid and 3-oxolupenal were investigated for their ability to inhibit α-amylase and α-glucosidase enzyme and found excellent inhibitory effect on both enzymes which proved the *N. oppositifolia* antidiabetic ability (Alqahtani *et al.,* 2019). Similarly, different solvents including hexane, ethanol, ethyl acetate and aqueous extracted *B. ferruginea* extracts was examined for antidiabetic property by important diabetic related enzymes such as α-glucosidase, α-amylase and lipase enzymes inhibition after treatment (Oyebode *et al.,* 2022). The above results revealed the various solvent extracted *P. pinnata* flower extract showed potent antidiabetic activity.

The various risk factors are commonly involved in the development and progression of DM including some metabolic disorders and oxidative stress. More importantly, oxidative stress, played major role in DM development and causes diabetic complications which linked to hyperglycaemia leads oxidative stress imbalance which is major reason for glucose homeostasis, inflammation and cell survival. In DM, the oxidative stress was induced by hyperglycemia through various molecular and biochemical process (Dave and Kalia, 2007), resulting severe complication of DM owing to enhanced free radicals and decreased antioxidant enzymes (Rajendran *et al.,* 2011). Antioxidants are major defence mechanism present in body against all free radicals and they acted by preventing or eliminating the toxic cells (Nishikawa *et al*., 2000; Sri Bhuvaneswari *et al*., 2023). Therefore, our study investigated the antioxidant property of methanolic extract of *P. pinnata* flower extract and found the potent antioxidant properties through various biochemical assays. Our study was supported by many works wherein, the methanolic extract of *P. pinnata* leaf was investigated for antioxidant property through *in vivo* method using Wistar rat to understand the various mechanisms involved in wound healing and found effective antioxidant activity by inhibiting lipid peroxidation, reduction in glutathione, increased catalase activity and reduced superoxide dismutase (Dwivedi *et al*., 2016; Al-Ansari *et al*., 2023). Similarly, the antioxidant property was studied for various solvents extracted like aqueous methanol, aqueous ethanol, absolute methanol, absolute ethanol, aqueous acetone, deionized water and absolute acetone *P. pinnata* bark, leaves and seeds and the maximum antioxidant components yield was found in bark extract followed by leaves and seeds. The various antioxidant assay revealed the potent activity due to the presence of phytochemicals like ferulic, gentisic, 4-hydroxybenzoic, ellagic, and protocatechuic suggesting the *P. pinnata* bark has strong antioxidant agents for pharmaceutical uses (Sajid *et al*., 2012; Sivakumar *et al*., 2022). In addition, the *P. pinnata* extract showed excellent hepatoprotective activity towards HepG2 cells. Overall, the study suggested that *P. pinnata* flower extract has strong inhibition on diabetic related enzymes and also, potent antioxidant activity as well as it has no toxic effect towards liver cells thereby no drug induced toxicity reveals *P. pinnata* flower extract can be a promising agent for DM.

5. Conclusion

The methanolic extracted *P. pinnata* flower extract had antidiabetic activity by inhibiting α-amylase and α-glucosidase enzymes and also has potent antioxidant activity by scavenging free radicals, nitric oxide, and ABTS. Moreover, the drug induced toxicity was investigated using HepG2 cells and showed no toxic effect towards liver cells. Overall, the activities exhibited by *P. pinnata* flower methanolic extract can be a promising agent for DM and their related complications.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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