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Comparative Analysis Of The Pharmacological Evaluation Of Tridax Procumbens Whole Plant Extract: Assessing In Vitro Antidiabetic And Nephroprotective Activities And Their Impact On Glucose Uptake And Dpp-Iv Inhibition

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KEYWORD

Tridax procumbens, Antidiabetic, Nephroprotective, *In vitro* studies, Natural remedies

ABSTRACT:

Through *in vitro* evaluations, this study explores the dual therapeutic potential of *Tridax procumbens*, examining its nephroprotective and antidiabetic properties. Examining the methanol extract of *Tridax procumbens* (TP-ME) revealed information about how it affected the dipeptidyl peptidase IV (DPP-IV) activity and how L6 myoblast cells utilised glucose.Although TP-ME had a slight antidiabetic impact, as demonstrated by a slight drop in serum levels of glucose and an upsurge in glucose absorption in L6 cells, the lack of a discernible DPP-IV inhibition calls for more research into the precise biochemical pathways at play. Concurrently, TP- ME's nephroprotective capacity is examined in relation to cytotoxicity in HEK-293 cellsinducedby cisplatin. Surprisingly, TP-ME exhibited a strong cytoprotective effect, and improving cell survival linked to kidney damage caused by cisplatin.These results highlight *Tridax procumbens'* potential in nephroprotective therapy by positioning it as a promising natural agent in reducing drug-induced kidney damage. *Tridax procumbens* presents itself as a versatile botanical candidate with potential applications in nephroprotective therapies and diabetic control. Deeper research into the precise bioactive chemicals in *Tridax procumbens*, their methods of action, and their potential benefits to reducing the global burden of diabetes and renal problems is warranted in light of the nuanced results seen *in vitro*.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorderhallmarked by higherlevels of blood glucose. It is a most importantcause of manycomplications that impact several organ systems. Nephrotoxicity due to chronic diabetes is often recognized as diabetic nephropathy. Diabetic nephropathyis one of the numerous complicationsassociatedwithlong term diabetes that significantly upsurges morbidity and mortality. Diabetic kidney disease (DKA) can cause gradual impairment in the renal system causing the kidneys to fail. The hallmarks signs of diabetic nephropathy are anomalies in the structure and function of the kidneys, which ultimately lead to reduced renal function[1-4]. Chronic hyperglycaemia, oxidative stress, and inflammation all have a role in the onset and development of nephrotoxicity in diabetes patients.The complex interaction of these variables may result in impairmentsin the renal tubules. These impairments can cause glomerular hyperfiltration, and enhanced permeability of the glomerular filtration barrier leading

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to chronic kidney disease. The use of renin-angiotensin-aldosterone system inhibitors, blood pressure control, and glycaemic control are the pillars of current therapeutic practices for diabetic nephropathy. Considering the present literature discussing the therapy of diabetic nephropathy,it can be stated that more recent, intensive,and efficient therapies are needed. A practical approach to making therapies that address the complicated pathophysiology of diabetic nephropathy is through natural resources. Many phytochemical compoundsare isolated and obtained from medicinal plants, including phenolic compounds, glycosides, terpenoids, flavonoids, and polyphenols. These phytochemical compounds have shown potential in reducing and neutralizing all the main factors that contribute to nephrotoxicity viz, oxidative stress, inflammation, and fibrosis[5-7].Growing body of research has investigated the potential nephroprotective benefits of numerous plant-based compounds, which include green tea catechins, resveratrol (found in red wine and grapes), Lycopene (found in tomato, watermelon etc.) and curcumin (*Curcuma longa*). These phytochemicals may be able to delay or halt the progression of diabetic nephropathy by modulating various signalling pathways involved in inflammation and fibrosis. Furthermore, oxidative stresscan be diminishedor neutralized by the antioxidant potential of these compounds. There is a significant correlation exists between diabetes, nephropathy, and cardiovascular disease as evident from literature. Some of these phytochemical compounds may demonstrateprotective action in cardiovascular system in addition to their capacity to diminish nephrotoxicity[3, 5-10]. Recent research in scientific literature shows promising outcomes from studies conducted on *Tridax procumbens* in labs and with animals. However, to turn these findings into practice as clinical therapies for people, it is important to carry out clinical trials involving humans.

Tridax procumbens L., although considered a weed in various crops, has a long history of being used as a traditional remedy for bronchial catarrh, diarrhoea, dysentery, and liver diseases in many countries across Africa, South, and Southeast Asia. The plant contains several bioactive compounds, including procumbetin, a few flavones includingglucopyranosyl and trimethoxyflavone, centaurein,centaureidin andpuerarin. Additionally, several phytoconstituents of lipid origin were also found which include methyl β-amyrin, methyl 14-oxononacosanoate, β-amyrone, 30-methyl-28-oxodotriacont-29-en-l-oic acid, fucosterol, 14-oxooctadecanoateand lupeol. Studies also reported the presence of severalphenolic acids in the plant which includebenzeneacetic acids, guiacol, benzoic acidandvanillic acid[11-13].

The plant, *Tridax procumbens* exhibits a wide range of biologicalas well as pharmacological activities. A strong larvicidal and allelopathic properties has been reported by the ethyl acetate extract of the plant. The alcoholic extracts have shown anti-hyperglycaemic, antileshmanial, hepatoprotective, antifungal, antibacterialand wound healing properties[14, 15]. The ethyl acetate extracthas also exhibitedantioxidant, protective and anti-inflammatory activities. Several other extracts including acetone fraction of the plant has been found to have anticoagulant, anti-hepatic, and antibacterial activities. However, there is currently no documented information on the anti-hyperuricemia property of *Tridax procumbens*[14, 15]. Despite being considered a weed, this plant has a rich medicinal history and is a source of various compounds with potential health benefits. Further research and documentation are needed, especially regarding its anti-hyperglycaemia and protective properties, to fully understand and utilize the therapeutic potential of *Tridax procumbens*[12, 13, 16].

Considering these therapeutic significance of*Tridax procumbens*, this present research work aimed to close the knowledge gap between traditional medicinal knowledge and contemporary scientific investigation[12, 13, 16]. This will empower the development of pioneering therapies for diabetes mellitus and its related complications in terms of diabetic nephropathy.This present study therefore has been designed to examine the *in vitro* antidiabetic and nephroprotective action of the whole plant extract of *Tridax procumbens* in various in vitro mechanistic models.

MATERIAL AND METHODS

Chemicals, Drugs, and Biochemical Kits

All the drugs, chemicals, reagents,and biochemical kitswere procured from reliable and pre-validated suppliers and vendors. The reagents and chemicals were of analytical grade.

Plant Material Collection and Evaluation

The candidate medicinal plant, *Tridax procumbens*was collectedfromKullu district of Himachal Pradesh. Dr. Ashok Kumar, a botanist with the Department of Botany, identified and authenticated the plant. A herbarium (accession number TPBKS15018/HP/022) of the plant has been made and deposited in the pharmacognosy laboratory of the aforementioned university department for future reference.

Extraction

The plant was dried in the shade for several days and then grinded into coarse powder using a mechanical grinder. The powdered crude drug of the plant (2.0 kg) was extracted progressively using four different

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solvents (Pet. ether, chloroform, acetone, methanol, and water) in a Soxhlet apparatus for several hours. All of the obtained plant extracts were concentratedin a rotatory vacuum evaporator (Perfit, India) at a temperature of < 50°C[17].All the five extracts - Pet. Ether (TP-PE), chloroform (TP-CE), acetone (TP-AE), methanol (TP-ME) and Water (TP-WE) - were kept at 4°C until use. The five extracts were subjected to total phenolic contents assay. The percentage yields of all the extracts were calculated using the following standard formula[18]**:**

% Yield= Amount of extract (g)/ Amount of initial dry powder drug (g) ×100

Phytochemical Screening

All the extracts were subjected to preliminary phytochemical screening for detectionof phytochemicals present in the extract which includes alkaloids, glycosides, flavanoids, phytosterols, phenols, saponins, proteins, and carbohydrates etc. Standard phytochemical tests were used for the purpose [19].

Total Phenolic Compounds assay

The Folin-Ciocalteu(FC) method was used to assay the total phenolic contents in the extract[20]. Gallic acid as a standard phenolic compound was used and a series of dilutions (100 to 1000 microg/mL) were made for the gallic acid for drawing a standard curve. In the method, sodium carbonate was added to each solution after adding the Folin-Ciocalteu reagent. This mixture was then incubated for 120 minutes and theoptical density or absorbance has been measured for each solution at wavelength of 765 nm in a UV-Vis spectrophotometer. The standard curve was used for the total phenolic content estimation in the extracts and expressed asgallic acid (GAE) equivalents per gram of the sample.

Antidiabetic activity

Glucose Utilization on L6 Myoblasts: The Experimental Method

The techniques outlined elsewhere were utiized to ascertain the usage of glucose in L6 myoblast cells[21]. At a cell density of 4,000 cells/well, L6 cells were added to 104-well growth plates. Until they achieved 95% confluence, these cells were permitted to attach. Two rows were kept cell-free to act as blanks for the glucose utilisation test. The cells were cultivated for five more days after reaching 95 percent confluence in the growth medium, which was changed to DMEM containing 2 percent FBS. The analysis for glucose utilisation was conducted 48 hours before the growth media was refilled. Ten millilitres (10 µg/ml, 20 µg/ml, and 60 µg/ml) of plant extract were applied to individual wells for the glucose utilisation experiment. Furthermore, as a positive control, insulin was added to a different column at a concentration of 6 µg/ml. An extra 48 hours were spent incubating the cells in the extract's presence. Following the incubation period, a 26 µl incubation buffer was added to replace the used medium. This buffer was made up of 10 millilitres of glucose, 0.2 percent BSA, and diluted RPMI medium with PBS. After that, the mixture was incubated at 37°C for three more hours. After removing 6 µl of the incubation medium from each well, added the 220 µl of reagent glucose oxidase (Bayer) to each plate well in order to quantify the glucose concentration in the medium.Following a 20-minute incubation period at 37°C, the absorbance at 522 nm was determined using a Multiscanmicrotitre plate reader (Lab Systems). The difference between the wells with and without cells was used to compute the glucose usage. The percentage of absorption of glucose was calculated by contrasting it with the untreated control group. The MTT test was used to determine the representative well's cell viability [22].

DPP-IV Inhibition Assay

The DPP-IV inhibition assay was performed in accordance with the Al-masri et al., 2009 technique [23] with slight modification. In brief, 16 µl of a solution containing human recombinant DPP-IV enzyme (55 µU/µl in Tris buffer) was introduced into the designated wells of a 104-well plate. This was accompanied by the addition of 36 µl of TP-ME (ranging from 60 µg/ml to 120 µg/ml) or a disease pr activity control (60 µg/ml of positive control, diprotin A). To recruit and start the reaction, 55 µl of Gly-Pro-ρNA (ρNA substrate) at 22 mM dissolved in Tris-buffer had been introduced after a 7-minute incubation at 37°C, followed by an additional 35-minute incubation at the same temperature. Subsequent to the incubation period, the reaction was halted by the addition of 26 µl of a 24% acetic acid solution, and the absorbance at 411 nm was recorded. Furthermore, a sample blank and a blank had been created via replacing 36 µl of the buffer system with TP-ME and 16 µl of the buffer with the enzyme, respectively. The inhibition percentage of the enzyme was
computedemploying the subsequent formula:

% inhibition = (Control Absorbance – TestAbsorbance) / Control Absorbance × 100

Nephroprotective activity

Effect of TP-ME in cisplatin-induced toxicity in HEK-293 cells

The human kidney embryonic cell line (ATCC; HEK-293) was utilised in the investigation. The cellshad been culturedin DMEM added with a 12% foetal bovine seruminactivatedby heat in a carbon dioxide incubation chamber (CO_2, 6%) at 37°C. Trypsinization was performed on the cells that were 80–90% confluent, and enough medium was supplied to stop the trypsin's

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action. Then the cells have been subjected to centrifugation for five minutes at 1400 rpm, the supernatant was discarded, and the pellet was reconstituted in medium before being counted using the Trypan blue exclusion method on a hemacytometer. To obtain the required number of cells, the cells were diluted with medium.In a 104-well microtiter plate with a flat bottom, the final seeding density for cell growth studies was maintained at 9000 cells per well. After seeding for 26 hours, the cells had beenkept as treatment added, non-treated, or cotreated for 26 hours with 20µM of cisplatin (CP) and TP-ME (10, 20, 50, 90, 140, and 200 µg/mL). Cell viability assay were carried out 26 hours after the start of therapy[24, 25].

Cell viability test

Tests for cell viability included the MTT [3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay. This MTT assay offers a delicate evaluation of the regular metabolic condition of cells. Following treatment, the corresponding treated cell wells were filled with MTT solution (6 mg/ml), which was then incubated for three hours. The formazan (darkblue coloured)formed in the end had been dissolved with DMSO solvent followed by measurement of the absorbance at 572 nm using a microtiter plate reader.

Statistical analysis

GraphPad Instat version 6 was used to undertake the statistical evaluation of the data. The data were presented as mean ± SD (standard deviation), and the One-Way Analysis of Variance (ANOVA) and Turkey *Post Test* were used to compare the various means. When $P < 0.05$, values were deemed to differ substantially (Software, 2013). For plotting the graphs GraphPad Prism Version 7 was used.

RESULTS AND DISCUSSION

Phytochemical Screening

To determine the existence of different bioactive chemicals, phytochemical assays were performed on aqueous, methanol, ethanol, chloroform, and acetone extracts of a specific plant (Table 1). The methanol, ethanol, and aqueous extracts all tested positive for alkaloids, indicating that these extracts may contain alkaloids. All of the extracts included carbohydrates, more especially reducing sugars, suggesting a compositional similarity. The aqueous, methanol, and ethanol extracts included phytosterols, which are substances that may have health advantages; the chloroform and acetone extracts did not contain any phytosterols.The aqueous and methanol extracts included flavonoids, which are recognised for their antioxidant qualities; only the acetone extract showed this component among the non-polar solvents. All extracts save the acetone extract included terpenoids, which have a variety of biological functions. Proteins were found in the methanol and aqueous extracts. Notable findings among the various extracts were the absence of glycosides, saponins, tannins, and phenols. These phytochemical results provide information about the plant's possible medicinal qualities, and differences in the presence of certain compounds suggest that using a variety of solvents is necessary for a thorough phytochemical examination.

Tablet 1. The results of the preliminary pharmaceutical screening for all the extracts

Phytochemical test	Aqueous extract	Methanol Extract	Ethanol Extract	Chloroform Extract	Acetone extract
Alkaloids					
Carbohydrates	+		+	+	+
Phytosterols	+		+	+	-
Glycosides	-		-	-	-
Flavonoids	+		+	-	+
Saponins	-		-	-	-
Phenols	+		+	-	-
Tannins	-		-	-	-
Proteins	+		+	-	+
Terpenoids	+		+	+	-

Total Phenolic Compounds assay

Gallic acid equivalents (GAE) per gramme of extract were used to express the total phenolic content (TPC) of the different extracts. The regression equations for TP-PE, TP-CE, TP-AE, TP-ME, and TP-WE were $y = 0.0024x + 0.0586$, $y = 0.0027x + 0.1074$, $y = 0.0027x + 0.0951$, $y = 0.0027x + 0.0951$, and $y = 0.0026x + 0.081$, in that order. The formulas provided enabled the determination of the total phenolic content in each extract. With 304.48 GAE per gramme, TP-ME had the highest total phenolic content, closely followed by TP-AE (281.08 GAE per gram). TP-PE displayed a slightly lower content of 209.45 GAE per gram than TP-CE and TP-WE, which displayed values of 212.91 and 198.67 GAE per gram, respectively. These findings highlight the wide differences in phenolic content between

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various extracts, indicating that the yield of bioactive phenolic compounds is highly dependent on the extraction solvent used (Table 2).

Table 2. The total phenolic contents for all the extracts

Extracts	Regression Equation	Total Phenolic content in GAE per gram of extract
TP-PE	y = 0.0024x + 0.0586 R^2 = 0.9677	209.45
TP-CE	y = 0.0027x + 0.1074 R^2 = 0.9248	212.91
TP-AE	y = 0.0027x + 0.0951 R^2 = 0.9398	281.08
TP-ME	y = 0.0027x + 0.0951 R^2 = 0.9398	304.48
TP-WE	y = 0.0026x + 0.081 R^2 = 0.9532	198.67

Antidiabetic activity

Glucose Utilization in L6 Myoblast

At all concentrations examined, TP-ME exhibited only minimal efficacy in reducing blood glucose levels in L6 myoblast cells (refer to Figure 1). In comparison to the majority of cases in the treated control group, TP-ME (107.62±2.61 percent) also exhibited a minor enhancement in absorption of glucose by L6 cells, although this effect was notably weak at the maximumtried concentration (60 µg/ml), where it reached 100 percent. In contrast, a positive control, insulin (6 µg/ml) had been employed and demonstrated a more substantial encouragementof glucose uptake in L6 cells, yielding a retort of 134.67±3.10 percent. As depicted in Figure 1, both the extract and insulin treatments on L6 cells, as evaluated by the tetrazolium based MTT technique of assay, showed no indication of possibledamage. Additionally, it was noted that, in contrast to the control, the extract and insulin significantly affected L6 cell proliferation for glucose absorption at every concentration examined.

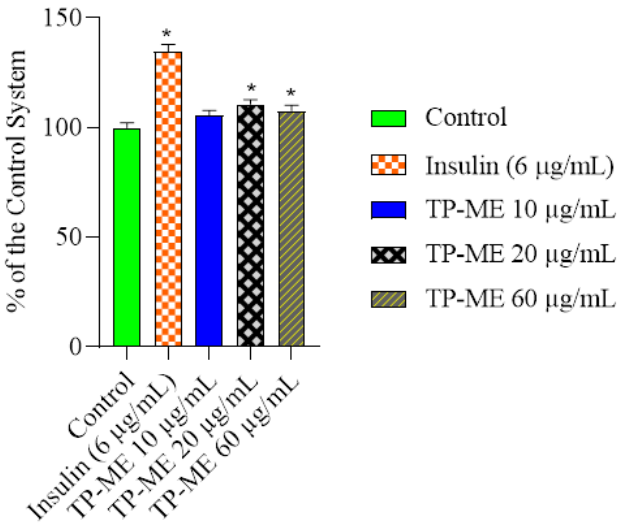

Figure 1. Impact of TP-ME on L6 myoblast glucose uptake. The plant extract was applied to the cells either at a constant concentration or at different concentrations for 48 hours.

Inhibition Assay of DPP-IV

When TP-ME was evaluated at each concentration, it showed a discernible but somewhat less inhibition than diprotin A, the positive control, which showed an inhibition of 82.67±1.87 percent against DPP-IV activity (as illustrated in Figure 2). However, there was a notable and significant suppression observed with the extractcompared to the non-treated control.

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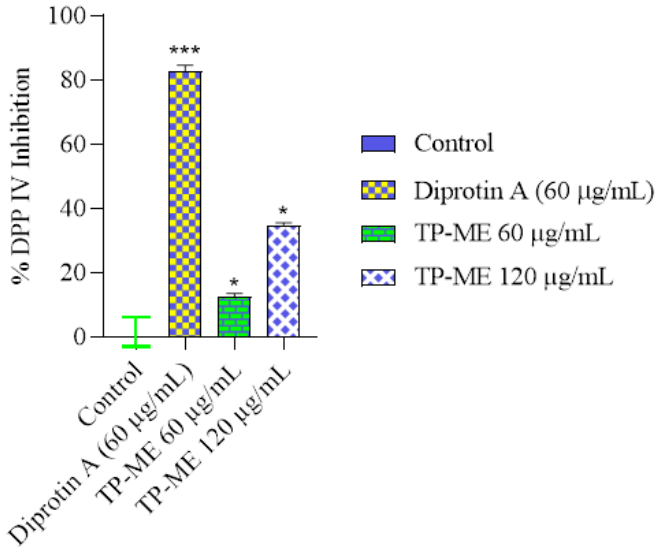

Figure 2. The effect of TP-ME on % inhibition of DPP-IV activity.

Nephroprotective activity

Result of impact of TP-ME in nephrotoxicity in HEK-293 cell Lineinducedby cisplatin

The effectiveness of the TP-ME in terms of nephroprotection was appraised using nephrotoxicity model in human embryonic kidney (HEK-293) cells induced by cisplatin. The viability of cell assay was performed to determine the nephron-cytoprotective effect of TP-MEin human embryonic kidneycells treated with cisplatin.The cells were exposed to varying TP-ME concentrations (10, 20, 50, 90, 140, and 200 µg/mL) for a whole day, either without or with 20 µM of Cisplatin. The TP-ME therapy by itself has no appreciable detrimental effects on cell viability. Treatment with cisplatin dramatically reduced the viability of the cells in comparison to a normal control ($P<0.001$).Cells treated with TP-ME and CP together greatly increased in viability. When TP-ME therapy was applied instead of cisplatin control, the cell viability increased by 7–25 percent. 9.585 µg/mL was found to be the EC50 (Figure 3).

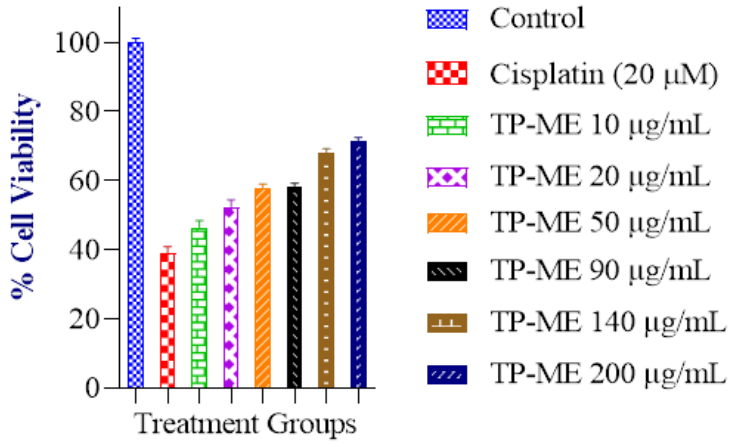

Figure3. Effect of TP-ME in nephrotoxicity induced by cisplatin in HEK-293 cells.

DISCUSSIONS

Through in vitro tests, the study investigated *Tridax procumbens'* nephroprotective and antidiabetic properties, providing insight into possible therapeutic uses. The Tridax procumbens methanol extract (TP-ME) showed marginal potential in reducing blood glucose levels in L6 myoblast cells during the evaluation of its antidiabetic action, with a minor

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increase in glucose uptake, especially at lower concentrations. Remarkably, the impact was not as strong as the untreated control system at the uppermost dosage tested (60 µg/ml). As a positive control, insulin, on the other hand, showed greater stimulation of glucose uptake, suggesting that TP-ME may have a less significant effect than insulin. Crucially, the MTT assay showed no evidence of TP-possible ME's toxicity on L6 cells, indicating the substance's safety profile when it comes to glucose utilisation.

Additionally, the study looked into the ways TP-ME inhibited DPP-IVenzyme in the metabolism of glucose. It was unexpected that TP-ME did not significantly decrease DPP-IV activity at any of the tested doses. The absence of inhibition compared to diprotin A, the control, raises questions about the mechanisms underlying the antidiabetic effects of TP-ME. This study investigated the effect of TP-ME in the damage caused by cisplatin in HEK-293 cells. First, checked if TP-ME itself had any harmful effects on the cells and found that it didn't cause any harm, suggesting that renal cells can use it safely and effectively. When cisplatin was used alone in a positive control cells, it significantly decreased cell viability and caused damage. However, when TP-ME was used alongside cisplatin, it increased cell viability by up to 25%, showing a protective effect against cisplatin-induced damage. The study observed this effect at a concentration of 9.585 µg/mL. The results for this research work demonstrated important findings regarding the protective effect of *Tridax procumbens*. TP-ME demonstrated weak DPP IV activity but significant effects on glucose utilization for diabetes. The extracts revealed significant protective action against Cisplatin induced nephrotoxicity. Further studies will be needed to fully explore the huge therapeutic potential of this plant. For the same future research may include evaluation of nephroprotective and antidiabetic activities in suitable animal models *in vivo* followed by the isolation of the responsible phytochemical components in *Tridax procumbens*.

CONCLUSIONS

In summary, research this have explored the potential uses of *Tridax procumbens* methanol extract (TP-ME) for kidney protection and managing diabetes. TP-ME had a modest effect on lowering blood sugar levels compared to insulin, especially in L6 myoblast cells' glucose utilization. The limited inhibition of DPP-IV activity raises interesting questions about how TP-ME works for diabetes. Since natural extracts have a mix of bioactive phytochemicals, more studies are needed to understand how TP-ME's components work together. For kidney protection, TP-ME showed a positive effect on damaged HEK-293 cells from cisplatin. The increase in cell survival and changes in cell shape suggest TP-ME could help reduce kidney injury. This finding opens the door to exploring *Tridax procumbens* as a natural treatment, especially for drug-induced kidney issues. However, it is crucial to note the limitations of lab-based research, even though *Tridax procumbens* shows promise. These discoveries have implications for human health, prompting further research through live organism studies (in vivo) and, eventually, clinical trials. Overall, *Tridax procumbens* seems promising for renal protection and managing glucose levels. Despite the mentioned limitations, this research provides a strong reason to study the specific phytochemicals in *Tridax procumbens*, how they work, and their potential for treatment. Using natural resources like *Tridax procumbens* could lead to new ways of managing renal issues and diabetes, addressing the need for safe and effective therapies in these areas.

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