

ABSTRACT

Current study was designed to explore the antioxidant and antidiabetic potential of *Cycas revoluta* (*C. revoluta*) and *Cycas circinalis* (*C. circinalis*) leaf extracts due to their use in local medicinal system as possible natural candidates for the management/treatment of diabetes mellitus. The extraction was optimized using different combination of water and ethanol (Aqueous, 20% ethanolic, 40% ethanolic, 60% ethanolic, 80% ethanolic and pure ethanol). For both the plants, 60% ethanolic extracts were revealed to be the most potent with optimal antioxidant and antidiabetic effects. The highest extract yields of $19.27 \pm 0.07\%$ and $20.97 \pm 0.20\%$ were obtained with 60% ethanol for *C. revoluta* and *C. circinalis*, respectively. The highest total phenolic contents i.e., 125.33 ± 1.28 and 154.24 ± 3.28 mg gallic acid equivalent per gram dry extract were observed for leaf extract of *C. revoluta* and *C. circinalis*, respectively, whereas total flavonoid contents of ethanolic extracts of *C. revoluta* and *C. circinalis* were 58.20 ± 1.34 and 78.52 ± 1.65 mg rutin equivalent per gram dry extract, respectively being the highest. The 60% ethanolic extracts of both plants also exhibited highest 2-diphenyl-1-picrylhydrazyl activity, total antioxidant power, beta carotene bleaching and iron chelating activity. The IC_{50} value for 60% ethanolic extract of *C. revoluta* to inhibit α -glucosidase was 66.80 ± 2.45 $\mu\text{g/mL}$ and for *C. circinalis* was 58.42 ± 2.22 $\mu\text{g/mL}$. The α -amylase inhibitory values for 60% ethanolic extract of *C. revoluta* and *C. circinalis* were also higher i.e., 82.01 ± 2.1 and 74.11 ± 1.7 , respectively. The statistical analysis indicated that the values of extract yields, antioxidant activities and enzyme inhibition were significantly higher for 60% ethanolic extract ($p < 0.05$). The proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra of *C. revoluta* and *C. circinalis* confirmed the presence of polyphenols due to peaks in relevant regions. The ultra-high performance liquid chromatography equipped with mass spectromometer (UHPLC-QTOF-MS/MS) analysis confirmed the presence of apigenin diglucoside isomers, kaempferol derivative, hexadecenoic acid and citric acid in 60% ethanolic extract of *C. revoluta* while iridoid glucoside, gibberellins A4, O-beta-D-glucosyl-4-hydroxy-cinnamate, 3-methoxy-2-phenyl-4-H-furo (2,3-h) chromen-4-one, kaempferol, withaferin A, amentoflavone, quercetin-3-O-(6''-malonyl glucoside), ellagic acid and gallic acid in *C. circinalis* leaf extract. The binding energy data obtained by molecular docking also confirmed the the possible role of identified metabolite to interact/inhibit the α -glucosidase and α -amylase enzymes. The extract dose of 500 mg/kg b.w. of both the plants lowered the blood glucose level of alloxonated mice sufficiently and comparable to attenuation caused by metformin. Improvement in lipid profile was also observed but not much effective as was the case with blood glucose. However, the antioxidant and antidiabetic efficiencies for *C. circinalis* were slightly pronounced than *C. revoluta*. Both the plants are proved as good source for naturopathic treatment of diabetes most probably due to possible synergistic impact of secondary metabolites, hence may be extended for pharmacological and functional food development in future.