

Antidiabetic effect of potential Indian medicinal plants: A target specific in-vitro study

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Abstract: Thirty plant species were selected from the published literature as traditionally used by the indigenous people of the Telangana State for common human ailments. Antioxidants present in plants play an important role to protect the human body against damage by reactive oxygen species. In present studies methanolic extract of 30 plants were analyzed in a DPPH assay of free radical scavenging activity and some of the extracts were found to possess activity comparable to ascorbic acid. The plant extracts having higher antioxidant activity are *Phyllanthus madaraspatensis*, *Bauhinia racemosa*, *Alkanna tinctoria*, *Ventilago maderaspatana* (94.29, 88.13, 66.87 and 100 % inhibition, respectively and IC₅₀ values recorded were 5.48, 9.25, 20.15, 60.15 µg/ml respectively, while the IC₅₀ value of standard compound (Ascorbic acid) is 20.9 µg/ml. In present studies 23 plant methanolic extracts were assayed for α-glucosidase enzyme inhibition activity of which 5 plant extracts i.e., *Jatropha gossypifolia* (59.95), *cocos nucifera* flowers (63.78), *Oroxylum indicum* (93.24), *Euphorbia hirta* (62.56) and *Cochlospermum gossypium* (62.69%) noticed with higher % inhibition and comparable with acarbose. IC₅₀ values of all five plant extracts were recorded as 2.83, 3.42, 0.72, 2.91, 1.9 µg/ml respectively while standard IC₅₀ value is 0.69 µg/ml for Acarbose. In present studies 30 higher % inhibition found were *Jatropha gossypifolia* (77.95%), *Hiptage mandablota* (82.16%), *Alkanna tinctoria* (86.32%), *Euphorbia hirta* (100%) and *Pterocarpus marsupium* (75.62%). IC₅₀ values of the plants recorded as *Pterocarpus marsupium* 55.81, *Jatropha gossypifolia* 50.23, *Hiptage mandablota* 20.76 and *Euphorbia hirta* 60.14 (µg/mL). Our data indicated that these plants could be potential natural sources for further drug development in diabetes.

Keywords: Medicinal plants; Diabetes; Alfa-glucosidase enzyme inhibition; AGE inhibition; Antioxidant activity.

I. Introduction

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. Diabetes mellitus is considered a major health concern, as its incidence is increasing at an alarming rate, and the high invalidating effects of its long-term complications affect macro- and microvasculature, heart, kidney, eye, and nerves. Increasing evidence indicates that hyperglycemia is the initiating cause of the tissue damage occurring in diabetes^[2]. Therefore, one therapeutic approach for treating diabetes is to control the hyperglycemia by reducing the absorption of glucose by inhibiting α-glucosidase. Enzyme alpha-glucosidase present in the epithelial mucosa of small intestine cleaves glycosidic bonds in complex carbohydrate to release absorbable monosaccharides. Inhibition of alpha-glucosidase in the digestive tract delay carbohydrate digestion and prolong overall carbohydrate digestion time, causing a reduction in the rate of glucose absorption and consequently blunting the postprandial blood glucose and insulin levels^[4,5]. Thus alpha-glucosidase inhibitors may be an attractive therapeutic modality in type 2 diabetic patients. Reduction of advance glycation end products (AGEs) and oxidative stress in different tissues might be other appropriate approaches beside reduction of hyperlycemia. AGEs are formed in vivo through a non-enzymatic glycation of glucose and other reducing sugars with proteins via so-called Maillard reaction. Hyperglycemia and free radical formation are characteristics of diabetes which accelerate the formation of advanced glycation end products (AGEs)^[5]. AGEs may produce reactive oxygen species (ROS), bind to specific cell surface receptors, and form cross-links^[1,3]. AGEs accumulate in the vessel wall, where they may perturb cell structure and function. AGEs have been implicated in both the microvascular and macrovascular complications of diabetes. AGEs may modify the extracellular matrix (ECM), modify the action of hormones, cytokines, and free radicals via engagement of cell surface receptors; and impact the function of intracellular protein. Oxidative stress in cells is

directly correlated with AGE formation. Many micro and macro complications of diabetes are related to oxidative stress. Low antioxidant level is associated with high AGE formation. Thus supplementation of plant based antioxidants may be useful to reduce the complications of diabetes.

Plant-based traditional medical systems continue to provide the primary health care to more than three quarters of the world's population. Indigenous herbal drugs widely used to treat diabetes and metabolic disorders. Plants continue to play an important role in the treatment of various diseases due to multiple beneficiary compositions having lesser or no side effect, and plant-based medicines can be used as an alternative approaches to treat diabetes. Traditional lifestyle, in which diet, exercise and possibly antioxidant and hypoglycemic medicines played an important role, may have masked people in pre-diabetic state in the past. As an evaluation of the benefit of the traditional medicine in relation to diabetes, we chose to study three types of activities in those plants used by the indigenous peoples of the South India for any symptoms associated with diabetes or its complications, on the premise that a particular species has a greater potential to treat diabetes if it can reduce more number of symptoms of diabetes or its complications.

Therefore the aim of our study was to evaluate the antidiabetic and antioxidant properties of 30 traditional plants of southern part of India. Our data indicated that out of 30 plants we screened, five of them have significant alfa-glucosidase inhibition properties, five of them have AGE inhibition properties and four of them have antioxidant properties.

II. Materials and Methods

2.1. Reagents

1,1-diphenyl-2-picrylhydrazyl (DPPH), methanol, glucose, BSA (Bovine serum albumin), sodium phosphate buffer, ascorbic acid, ethanol, para-nitrophenyl-alpha-D-glucopyranoside, ascorbic acid.

2.2. Plant material

The plants were selected on the basis of their known medicinal activities in southern part of India. These plants were known to possess different type ethano medicinal properties. 30 medicinal plants were collected from Andhra Pradesh state and authenticated by Department of Botany, Kakatiya University Warangal. All plant species were collected in the month of October -November 2012.

2.3. Extraction procedure

Samples were air dried in shade before grinding to a particle size of 850 μ m. Some of the thicker root samples and market produce were frozen and dried lyophilization before grinding. Extractions were performed in distilled methanol solvent using a Soxhlet apparatus. A fifty gm of each part's powder (leaf, stem or root) was extracted with 400 mL methanol by soxhlet percolation for 48 hrs. Extracts were collected and filtered twice using Whatman No.1 filter paper. The filtrates were then concentrated by rotary evaporation under reduced pressure at 40°C. Next the concentrates were poured into glass petri-dishes and put in the oven at 60° C for further drying and the resulting paste was stored in cold until further use.

2.4. Alfa-glucosidase inhibition assay.²⁰

Intestinal alpha-glucosidase inhibition activity: 20 μ l of plant extracts (5mg/ml) was incubated with 50 μ l of crude intestinal alpha glucosidase for 5 minutes, and then 50 μ l of substrate 5mM para-nitrophenyl-alpha-D-glucopyranoside. Absorbance was measured at 405nm. Percentage enzyme inhibition was calculated. The formula is = Control- Sample/Control \times 100.

2.5. Advanced glycation end product inhibition assay.²¹

For measurement of AGE, 40 μ l of the plant extract were added in 100 μ l of glucose and 60 μ l of BSA and made up the volume up to 200 μ l with sodium phosphate buffer in an eppendroph tube. Incubated the above solution for 12hrs at a temperature of 50°C in a water bath. The fluorescence was measured by using emissions at 440nm upon excitations at 370nm. (Munch et al., 1997).

2.6. DPPH radical scavenging activity Assay.²²

The DPPH scavenging activity was determined by an assay modified from Khatua et al., 2012. DPPH solution was prepared at the concentration of 0.195 mg/ml in methanol. To 150 μ l of DPPH solution, 20 μ l of plant extract (range 20 to 1000 μ g/ml) was mixed and kept in the dark at room temperature for 60 minutes. After incubation, the absorbance was recorded at 517 nm. The results were compared with the control which contained 50 μ l of ethanol instead of plant extracts. The positive control used for this study was ascorbic acid. The antioxidant activity was expressed as percentage (%) inhibition = $\{($ absorbance control 517 nm – absorbance of samples 517nm) / absorbance of the control 517nm $\} \times 100$.

2.7. Statistics

All samples were analyzed in triplicate. Data are presented as mean \pm standard error mean (SEM). Differences were evaluated by one-way analysis of variance (ANOVA) test completed by a Bonferroni's multi comparison test. Differences were considered significant at $p < 0.01$. The concentration giving 50% inhibition (IC_{50}) was calculated by non-linear regression with the use of Graph pad Prism Version 5.0 for Windows (Graph Pad Software, San Diego, CA, USA) (www.graphpad.com) the dose-response curve was obtained by plotting the percentage inhibition versus concentration^[37].

III. Results

3.1 Alfa-glucosidase enzyme inhibition assay

During screening of 23 promising Indian medicinal plants in search of potent glucosidase enzyme inhibitors, 23 plant extracts were evaluated using Acarbose as standard for alfa-glucosidase enzyme inhibition assay. Among them five plant extracts exhibited significant inhibition in terms of IC_{50} values up to 3.42 μ g/ml compared to Acarbose 0.69 μ g/ml (Table 2), (Fig. 1)

3.2 Advance glycation end product inhibition assay

In search of potent advance glycation end products inhibitors, 30 plant extracts were evaluated in a non-enzymatic assay. Amongst these 5 plants extracts exhibited significant inhibition above 75% and IC_{50} values are given in Table 3 (Fig. 2)

3.3.DPPH free radical scavenging assay

All 30 plant extracts (Table-1) were evaluated for antioxidant activity. The extracts are able to reduce the stable radical DPPH to the yellow-coloured diphenylpicrylhydrazine. The scavenging effect of methanol extracts and standards with the DPPH radical is given in Table 4. Among them, four plants have shown comparable IC_{50} values and it is significant to note that two of them are much more potent than ascorbic acid (Table 4). The reduction capability of DPPH radical is determined by the decrease in absorbance at 517 nm induced by antioxidants. Ascorbic acid is used as standard compound (Fig. 3).

IV. Discussion

Different alfa-glucosidase inhibitors such as Oleanolic acid and its semi synthetic derivatives⁷, phenolic compound from aqueous extract of *Myrtus communis*⁹ Oroxylin A, a flavone from hexane extract of *Oroxylum indicum* plant,¹⁰ Nojirimycin and 1-deoxynojirimycin from Rosell (*Hibiscus sabdariffa*) and leaves of *Morus bombycis*¹¹ reported from plant sources, Acarbose- Glycolipids, Miglitol – Glyset – Glycerol and Derivatives, Piperidines, Voglibose - Glycerol and Derivatives⁸ are well-known and marketed. Present investigation revealed extracts of *Jatropha gossypifolia* bark, *Cocoss nucifera* flowers, *Oroxylum indicum* bark, *Euphorbia hirta* whole plant, *Cochlospermum gossypium* bark have exhibited remarkable activity. Therefore, based on bioassay guided information, further investigation is necessary in isolation, identification and characterization of bioactive principles.

AGEs inhibitors are phenolic compounds such as catechin, epicatechin and procyanidin B2 and phenol polymers from aqueous extract of cinnamon bark effectively scavenge reactive carbonyl species.⁴ A terpenoid compound, Labdadiene dial from hexane extract of *Alpinia zerumbet* rhizomes⁵ and a flavanol compound, mesquite from methanolic extract of *Dichrostachys cinerea* derived from plant sources. During our studies the extracts of *Jatropha gossypifolia*, *Hiptage madablota*, *Bauhinia racemosa*, *Alkanna tinctoria*, *Euphorbia hirta*, *Oxalis corniculata* have exhibited remarkable AGEs inhibition activity.

Well known and recognized dietary antioxidants are vitamin C, vitamin E, selenium, and carotenoids. However, recent studies have demonstrated that flavonoids found in fruits and vegetables may also act as antioxidants. Present investigation on antioxidant activity by DPPH inhibition assay, the extracts of *Phyllanthus maderasipatensis*, *Bauhinia racemosa*, *Alkanna tinctoria* and *Ventilago maderaspatna* have shown significant IC_{50} values.

The reports on the preliminary phytochemical screening examination of *Cochlospermum gossypium* (bark), *Jatropha gossypifolia* (root), *Bauhinia racemosa* (root) on antidiabetic activity are not available till date except *Euphorbia hirta* (whole plant). *Euphorbia hirta* has been examined earlier for the phytochemical constituents and found to possess tannins, saponins, flavonoids, steroids, cardiac glycosides and alkaloids. Hence there is a need for further investigation to isolate, identify and characterize the active compounds from those plants which showed good antidiabetic property. Amongst them *Euphorbia hirta*, *Jatropha gossypifolia* and *Bauhinia racemosa* with multiple biological functions are the most promising and of great interest for further investigation in development of new potent multifunctional inhibitors in management of diabetic therapy.

V. Conclusions

Since it has been shown that the antioxidants, α -glucosidase enzyme inhibitors, advanced glycation end product inhibitors play important role and contribute to management of diabetes through different pathways, and plants being a treasury of source of various biologically active molecules. Our present studies conclude that it helped in identifying the promising plants with multiple biological functions which could be the potential source of unique bioactive therapeutic molecules for the management of hyperglycemia, diabetes and the related conditions warranting further investigation.

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Table :1 List of all plants along with their parts used and application in literatures

PLANT	FAMILY	PARTS AND USE
Acalypha indica	Euphorbiaceae	Herb, Skin diseases
Adahatoda vasaka	Acantheceae	Leaf, Tuberculosis
Acacia chundra	Mimocaceae	Bark, asthma, Fever
Alkanna-tinctoria	Boraginaceae	Skin infections
Aegle marmelos	Rutaceae	Fruit pulp, Dysentery
Bauhinia racemosa	Caesalpinaceae	Bark, Dysentery
Bixa orellana	Bixaceae	Seed pulp, Dysentery
Clerodendrum serratum	Verbenaceae	Plant, Asthma, bronchitis
Cochlospermum-gossypium	Bixaceae	Stem, Gum Wounds
Chloroxylon-swietenia	Rutaceae	Bark, Shivering, Neck pain
Cocos nucifera	Aracaceae	Seeds, Burns, hair loss
Diplocyclus-palmatus	Cucurbitaceae	Leaf, Fever
Erythrina indica	Fabaceae	Bark, Wounds
Euphorbia hirta	Euphorbiaceae	Leaf juice, Scabies
Hybanthus vatsavaya	Violaceae	Whole plant, Urinary diseases
Hiptage mandablota	Malpighiaceae	Leaf, bark, Cough inflammation, skin disease
Jatropha gossypifolia	Euphorbiaceae	Bark paste, Dog bite
Lantana camara	Verbenaceae	Shrub Constipation, fever & stop bleeding
Nelumbo nucifera	Nyamphaceae	Seed, infertility
Michelia champaka	Mangolaceae	Flower oil, Rheumatism
Melia dubia	Meliaceae	Paste of berries, Leprosy
Oroxylum indicum	Bignonaceae	Bark, Rheumatism

Oxalis corniculata	Oxalidaceae	Leaf juice, Dysentery
Phyllanthus maderaspatensis	Euphorbiaceae	Fruit powder, Teeth diseases
Pergularia-daemia	Asclepiadaceae	Leaf, Corneal opacity, gout, boils, blisters, wounds
Pterocarpus marsupium	Papilionaceae	Leaf, Diabetes, Labour pains
Smilax zeylanica	Smilacaceae	Root, Venereal disorders
Ventilago maderaspatana	Ramnaceae	Root, Stomachache
Wrightia-tinctoria	Apocyanaceae	Leaf, Boils, blisters, fever
Zanthoxylum rhetsa	Rutaceae	Spines, applied on breast to relieve pain

Table:2 Alfa-glucosidase enzyme inhibition assay

Compound no.	Compound name	% inhibition
1	Bixa orellana(L)	26.65%
2	Pergularia daemia (w.p)	NA
3	Chloroxylon swietenia(L)	51.72%
4	Jatropha gossypifolia	59.95%
5	Oxalis corniculata(w.p)	56.89%
6	Melia dubia(L)	59.69%
7	Michelia champaka(L ¹)	61.28%
8	Smilax zeylanica(R)	NA
9	Cocos nucifera (Fl)	63.78%
10	Acacia chundra(B)	NA

11	Aegle marmelos (R)	52.55%
12	Hybanthus vastavaya(w.p)	49.87%
13	Wrightia tinctoria (B)	22.96%
14	Lantana camara(L)	40.94%
15	Xanthoxylum rhetsa(B)	56.38%
16	Bauhinia racemosa(R)	35.52%
17	Aegle marmelos(L)	30.61%
18	Oroxylum indicum(B)	93.24%
19	Pterocarpus marsupium(B)	31.63%
20	Ventilago madraspatana(B)	56.25%
21	Euphorbia hirta(w.p)	62.56%
22	Cochlospermum gossypium(B)	62.69%
23	Alkanna tinctoria(R)	55.74%
Acarbose	Standard compound	93.97%

IC₅₀ value of α -glucosidase inhibitory assay

Compound no.	Compound name	IC-50 (μg/mL)
4	Jatropha gossypifolia (R)	1.84
9	Cocos nucifera (Fl)	2.91
18	Oroxylum indicum(B)	0.723
21	Euphorbia hirta(w.p)	3.421
22	Cochlospermum gossypium(B)	2.83

Standard	Acarbose	0.691
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Table 3:Advanced glycation end product assay

Compound no	Compound name	% inhibition
1	Pterocarpus marsupium(B)	75.62664
2	Adathoda vasaka(L)	5.37339
3	Xanthoxylum rhetsa(L)	66.31328
4	Bixa orinella(L)	29.17909
5	Jatropha gossypifolia (R)	77.95174
6	Melia dubia(L)	NA
7	Phyllanthus maderasipatensis(B)	43.73623
8	Lantana camara(L)	10.23355
9	Chloroxylon swietenia(L)	NA
10	Hiptage mandabloata(B)	82.16646
11	Acalypha indica(w.p)	NA
12	Michelia, champaka (L)	45.58439
13	Aegle marmelos (R)	NA
14	Smilax zeylanica(R)	4.025506
15	Clerodendrum serratum (B)	47.06187
16	Aegle marmelos(L)	24.22821
17	Bauhinia racemosa (R)	60.58218
18	Michelia champak(L ¹)	44.45683
19	Alkanna tinctoria(R)	86.32157
20	Erythrena indica (L)	NA
21	Oroxylum indicum(B)	NA

22	Acacia chundra(B)	NA
23	Cocos nucifera (Fl)	NA
24	Hybanthus vastavaya(w.p)	NA
25	Nelumbo nucifera(S)	25.33503
26	Ventilago madrasipatana(B)	NA
27	Euphorbia hirta(w.p)	100.2929
28	Wrightia tinctoria (B)	7.864382
29	Colchospermum gossypium(B)	NA
30	Oxalis corniculata(w.p)	63.1639

IC₅₀ value of AGE

Compound no.	Compound name	IC-50 (µg/mL)
1	Pterocarpus marsupium(B)	558.1149
5	Jatropha gossypifolia (R)	502.3077
10	Hiptage mandabloata(B)	207.6042
27	Euphorbia hirta(w.p)	601.408

Table 4: Antioxidant activity of all plant extract as assayed by DPPH inhibition assay

Compound no	Compound name	% inhibition
1	Pterocarpus marsupium(B)	43.7596302
2	Adathoda vasaka(L)	9.86132512
3	Xanthoxylum rhetsa(L)	44.375963

4	Bixa orellena(L)	43.4514638
5	Jatropha gossypifolia (R)	47.1494607
6	Melia dubia(L)	38.0585516
7	Phyllanthus maderasipatensis(B)	94.2989214
8	Lantana camara(L)	19.8767334
9	Chloroxylon swietenia(L)	46.6872111
10	Hiptage mandabloata(B)	38.2126348
11	Acalypha indica(w.p)	20.8012327
12	Michelia,champaka (L)	39.2912173
13	Aegle marmelos (R)	38.366718
14	Smilax zeylanica(R)	30.3543914
15	Clerodendrum serratum (B)	38.366718
16	Aegle marmelos(L)	29.7380586
17	Bauhinia racemosa (R)	88.1355932
18	Michelia champaka(L ¹)	37.7503852
19	Alkanna tinctoria(R)	66.8721109
20	Erythrena indica (L)	37.9044684
21	Oroxylum indicum(B)	37.1340524
22	Acacia chundra(B)	40.3697997
23	Cocos nucifera (Fl)	43.7596302
24	Hybanthus vastavaya(w.p)	33.4360555
25	Nelumbo nucifera(S)	35.9013867
26	Ventilago madrasipatana(B)	100
27	Euphorbia hirta(w.p)	38.5208012
28	Wrightia tinctoria (B)	40.8320493

29	Colchospermum gossypium(B)	36.6718028
30	Oxalis corniculata(w.p)	39.2912173
Standard compound	Ascorbic acid	81.78

IC₅₀ value of DPPH assay.

Compund no.	Compund name	IC-50 (µg/mL)
7	Phyllanthus maderasipatensis(B)	5.48
17	Bauhinia racemosa (R)	9.25
19	Alkanna tinctoria(R)	20.15
26	Ventilago madrasipatana(B)	60.15
Standard	Ascorbic acid	20.9

Abbreviations: R, Roots; B, Stem bark; L, Leaves ; Fl, Flowers ; S. Seeds; w.p , whole plant

Fig. 1

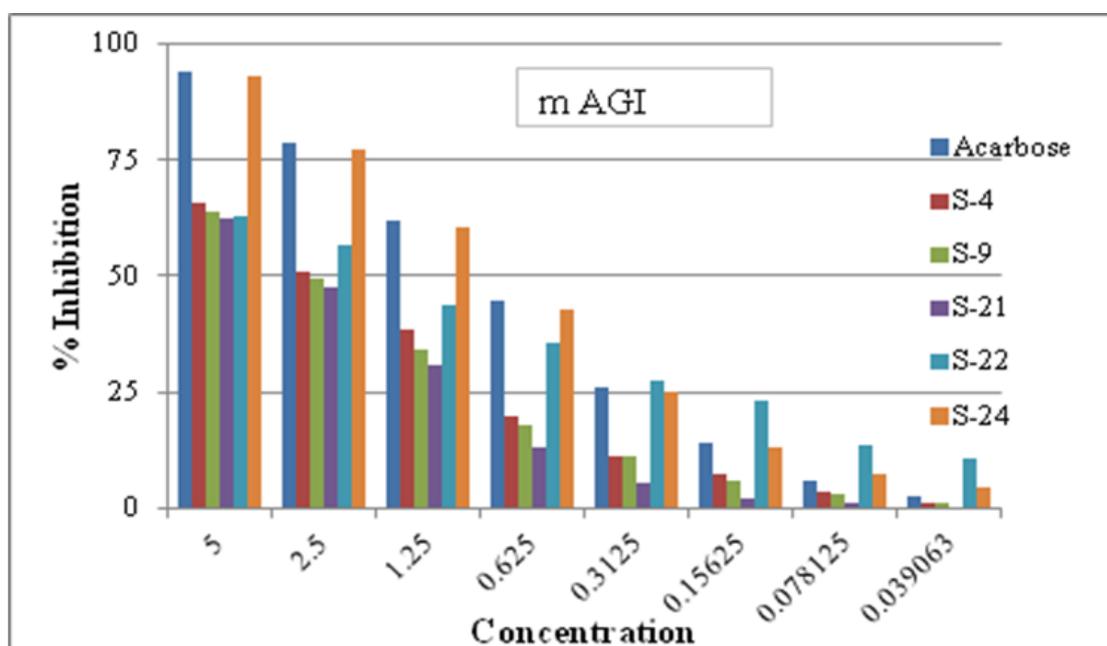


Fig. 2

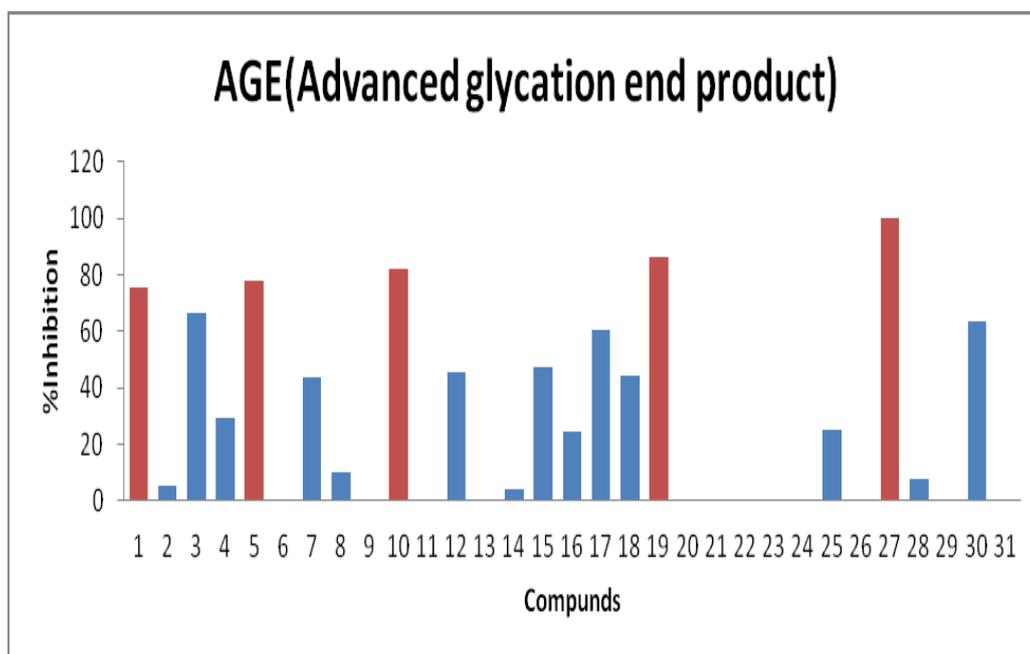
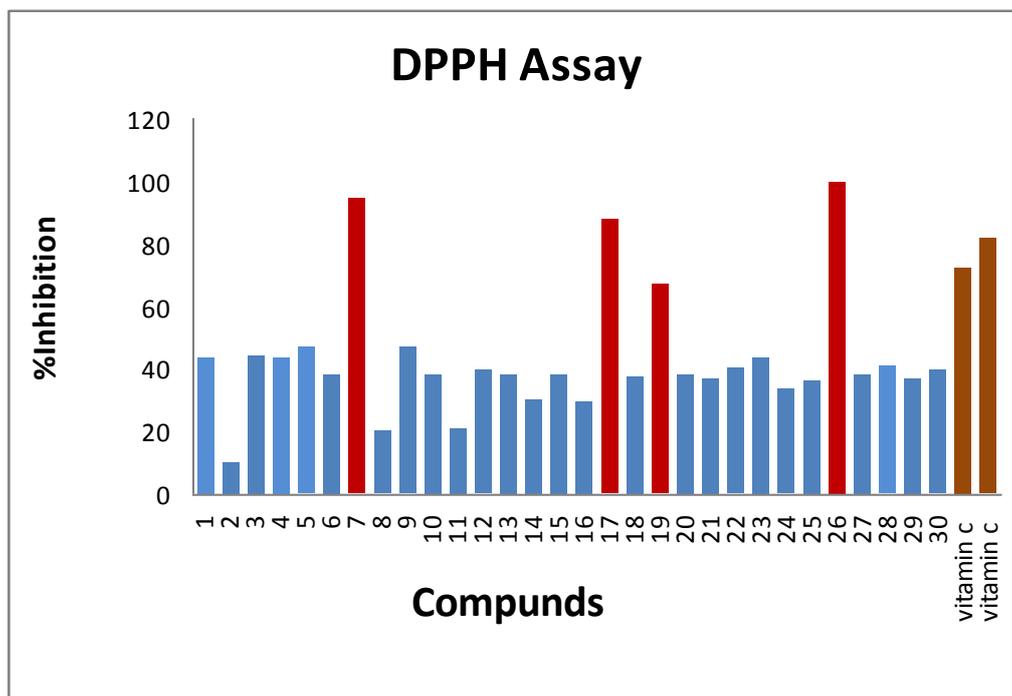


Fig. 3



Legends

1. The effects of 23 plant extracts on Alfa-glucosidase enzyme assay. The results were showed the % inhibition of Alfa-glucosidase enzyme.
2. The effects of 30 plant extracts on formation of advanced glycation end products (AGEs). The results were showed the % inhibition of AGE formation.
3. The effects of 30 plant extract on DPPH. The results were showed the % inhibition of oxidant activity.