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ORIGINAL RESEARCH ARTICLE

Chemoprofiling of *Artocarpus camansi* Blanco. and *Artocarpus lakoocha* Wall. ex. Roxb. and its antidiabetic potential for modulation of digestive enzymes, protein glycation and glucose uptake in L6 myotubes

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ABSTRACT

*Acetone extract of the stem bark of Artocarpus camansi and Artocarpus lakoocha afforded **14** compounds. Herein, we report the compounds **3, 8, 9, 10, 11, 12** and **13** for the first time from these species. The structures were elucidated on the basis of various spectroscopic analyses including IR, 1D and 2D NMR, and HRMS data. All the isolated compounds were tested for α-glucosidase, α-amylase and glycation inhibitory activity. Oxyresveratrol displayed prominent IC_{50} value of 37.38 ± 1.11 µM in α-glucosidase inhibitory assay. Compound **3, 4** and **8-13** exhibited moderate α-glucosidase inhibitory activity. The effect of glucose uptake performed by 2-NBDG in L6 muscle cells using fluorescent microscope and flow cytometry. The compounds E-resveratrol **(1)**, artobiloxanthone **(11)** and artonol B. **(13)** showed glucose uptake of 32.2 %, 32.9 % and 33.5 % respectively.*

INTRODUCTION

The genus *Artocarpus* (Moraceae) comprises about 50 species of evergreen and deciduous trees. A number of *Artocarpus* species are used as food and for traditional folk medicines in South-East Asia, Indonesia, Western part of Java and India (Perry, 1980; Heyne, 1987). *Artocarpus camansi* Blanco, (breadnut) has often been considered to be a seeded breadfruit belonging to Moraceae family and native to New Guinea and possibly in India. It is utilized as vegetable. The decoction of *A. camansi* leaves is used for diabetes and baths of people with rheumatism. It was also found to be an effective natural product to treat allergic contact dermatitis (Salonga et al., 2014). α-Sitosterol propionate isolated from the hexane extract of the leaves of *A. camansi* showed antidiabetic properties (Nasution et al., 2014). The extracts of

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A. camansi leaves were considered as highly cytotoxic against the selected human cancer cell lines (Ourlad Alzeus et al., 2015). Monkey Jack fruit (*Artocarpus lakoocha* Roxb. Moraceae) is a tropical fruit and originated from India. This fruit is a rich source of vitamins and minerals those act as antioxidant (Jahan et al., 2011). The genus *Artocarpus* is gaining lots of research attention in the recent times for its nutritional and health benefits. It has been established by research groups that the consumption of tropical fruits reduces the risk of fast-growing diseases like diabetes, cancer, coronary heart disease, neurodegenerative ailment (Rajurkar & Gaikwad, 2012).

Diabetes is a complicated chronic illness that requires intensive self-care management. It is evident from the literature that the role phytomolecules in antidiabetic drug discovery is increasing day by day (Subramoniam 2018). Most of the available drugs used for curing type 2 diabetes causes serious side effects such as obesity, urologic and sexual complications (Kahn et al., 2006). The pervasiveness of type 2 diabetes is growing globally, and thus there is need for new antidiabetic drugs with less side effects. The plant derived antidiabetic drugs available in market reveal the importance of phytochemicals to regulate this metabolic disorder, compelling the search for new naturally inspired antidiabetic drug candidates (Evans et al., 2002).

The *Artocarpus* species are rich in phenolic compounds including stilbenoids, flavonoids and arylbenzofurans (Hakim et al., 2006, Jagtap and Bapat, 2010). The biological activities such as anti-bacterial (Sato et al., 1996), antimalarial effects (Namdaung et al., 2006), antitubercular activity (Boonphong et al., 2007), antiviral activity (Likhitwitayawuid et al., 2005), antifungal activity (Trindade et al., 2006) and anti-inflammatory activity (Wei et al., 2005), make these phenolic compounds as a potential drug candidate. In the limelight of these reports and due to our continuing interest in the chemical profiling of the plants of ethnobotanical importance (Sasikumar et al., 2016, 2019). We selected the two plant species namely *A. camansi* (AC) and *A. lakoocha* (AL). Even though there are some literature reports on the isolation of phytochemicals from these plants (Nasution et al., 2014; Tsai et al., 2013), it is essential to conduct more scientific research on wild edible plants that can be further exploited for value added products in the form of nutraceutical and health products. Among these plants, to the best of our knowledge, the isolation of xanthone derivatives from the *A. camansi*, is unknown to the phytochemical research community.

MATERIALS AND METHODS

Plant material

The bark of *Artocarpus camansi* Blanco. and *Artocarpus lakoocha* Wall. ex. Roxb. were collected from Thrissur and Calicut, Kerala and deposited in M. S. Swaminathan Research Foundation, Wayanad, Kerala (Voucher no. M.S.S.H. 1631 and M.S.S.H 1801) respectively.

Experimental procedure

NMR spectra were recorded at 25^{o}C on 500 MHz BRUKER instrument. The ^{1}H and ^{13}C NMR chemical shifts were referenced to tetramethyl silane (TMS) as standard. HRMS (ESI) was recorded on a Thermo Scientific Exactive Column used: C18 reverse phase column. All solvents used for chromatography and HRMS were purchased from Merck (HPLC grade). For column chromatography, silica gel of different pore 100–200, 230–400 was used. For α-glucosidase and α-amylase inhibition assay, acarbose was used as the standard and ascorbic acid as the standard for antiglycation assay. Glucose uptake assay was performed by 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-2-Deoxyglucose) (2-NBDG) in L6 rat skeletal muscle cells using flow cytometry (BD FACS Aria II, USA). The effect of glucose uptake was compared with standard drug rosiglitazone, (Merck).

Enzymatic antidiabetic assays

α-Glucosidase inhibitory activity was performed according to the method reported by Adisakwattana et al., 2011. α-Amylase inhibition

activity was carried out based on the starch-iodine test in a microlitre plate (Xiao et al., 2006).

The α-glucosidase and α-amylase inhibitory activity was expressed as the inhibition percentage and was calculated as follows:

$$\% \text{ Inhibition} = \frac{\text{Absorbance of Control - Absorbance of Sample}}{\text{Absorbance of Control}} \times 100$$

Anti-glycation assay was performed according to the method reported by Jedsadayanmata, 2005 with slight modification.

Cell culture

Rat L6 skeletal muscle cells were grown in 25 mM DMEM with 10 % Fetal bovine serum and 10 % of 1X antibiotic antimycotic solution at 37°C under 5 % CO_2 atmosphere. To differentiate, cells were permitted to reach upto 70 % confluence, and the medium was replaced to medium containing 2 % Horse serum for 4-5 days, with medium changes in alternate days.

Cell viability by MTT

Myoblast viability and proliferation were examined with MTT. For the MTT assay, cells were treated with diverse concentrations of compounds for a period of 24 hours and then incubated with 5 mg/mL MTT for an additional 4 hours at 37°C. Medium was then decanted and 100 µL of DMSO was added for dissolving the formazan crystal produced. Absorbance was measured at a wavelength of 570 nm with a microplate reader (BIOTEK-USA).

2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-2-Deoxyglucose, *2-NBDG) Uptake*

L6 myotubes after 5 days differentiation seeded in 96 well black clear bottom plates were incubated with the least cytotoxic concentration of compounds for 24 hours in the presence of insulin (50 nM). Following incubation with compounds, culture medium was decanted from each well and substituted with fresh culture medium in the absence or presence of 100 µM 2-NBDG (Molecular Probes-Invitrogen), a fluorescent derivative of glucose and incubated for 30 min. PBS wash were given to cells following 2-NBDG treatment and the fluorescence in cells were obtained by a Fluorescent Microscope (Pathway 855, BD Bioscience, San Jose, CA, USA) and Laser Scanning Confocal microscope (Nikon A1R, Nikon instruments, Melville, USA) arranged with filters in the FITC range (excitation, 490 nm and emission, 525 nm).

The differences in glucose uptake stimulated by pretreatment of flavonoids were confirmed by flow cytometry examination. Following pretreatment, cells were treated in the presence or absence of 2-NBDG as explained above. The cells were then washed twofold with phosphate-buffered saline (PBS), subsequently exposed to trypsinization and resuspended in ice-cold PBS and subjected to flow cytometry analysis. Both labelled and unlabeled samples were studied using BD FACS Aria II (BD Biosciences) at FITC range (excitation 490 nm, emission 525 nm band pass filter).

RESULTS AND DISCUSSION

Biological screening of different extracts of A. camansi (AC) and A. lakoocha (AL)

The dried bark of AC and AL were subjected to extraction at room temperature with different solvents such as acetone and ethanol. These extracts were analysed for α-glucosidase, α-amylase inhibitory activity and antiglycation activity. The results from the study showed that the acetone fraction of AC (ACA) effectively inhibited α-glucosidase and α-amylase enzyme (IC_{50} 49.54 and 27.18 µg/mL), which is comparable to that of the standard acarbose (IC_{50} 45.37 and 5.53 µg/mL). The result from our study depicted that showed a prominent antiglycation property with an IC_{50} 4.90 µg/mL, which is better than (IC_{50} 48.00 µg/mL). The ethanol extract of AL (ALE) showed a prominent α-amylase inhibitory activity (IC_{50} 26.00 µg/mL) compared with (Table 1).

Table 1: Antidiabetic activity screening of different extracts of *A. camansi* (AC) and *A. lakoocha* (AL)[a]

Extracts	α-glucosidase (µg/mL)	α-amylase (µg/mL)	Antiglycation (µg/mL)
ACA	49.54 ± 0.34	27.18 ± 0.14	4.90 ± 0.20
ACE	81.31 ± 0.51	80.81 ± 0.57	95.26 ± 0.55
ALA	63.02 ± 0.51	265.44 ± 0.23	84.70 ± 0.57
ALE	64.28 ± 0.40	26.00 ± 0.26	85.64 ± 0.66
Acarbose	45.37 ± 0.68	5.53 ± 0.36	……
Ascorbic acid	……	……	48 ± 0.87

[a](A) acetone and (E) ethanol fractions. All data are represented as mean ± standard deviation (n=3)

Isolation and characterization of compounds

Based on the *in vitro* enzymatic antidiabetic activity of all the extracts and TLC analysis, further isolation, purification and characterization of chemical constituents were focused on the acetone extract. ACA (30 g) was fractionated on a silica gel (100-200 mesh) column and eluted with n-hexane 100 % to EtOAc 100 % gradient. Based on the TLC profile forty-five fractions (Fr.ACA.1-Fr.ACA.45) were collected. Fr.ACA 1-44 were further column chromatography over silica gel using a gradient solvent system of n-hexane-EtOAc and Sephadex LH-20 to give **12** major compounds; *E*-Resveratrol **1** (22 mg) (Lambert et al., 2013), Oxyresveratrol **2** (66 mg) (Takasugi et al., 1978; Hanawa et al., 1992), α-Amyrin acetate **4** (30 mg) (Okoye et al., 2014), Betulinic acid **5** (32 mg) (Bisoli et al., 2008; Bringmann et al., 1997), Cycloartenol acetate **6** (230 mg) (Teresa et al., 1987), Cycloartenol **7** (135 mg) (Teresa et al., 1987; Tsai et al., 2013), Artocarpesin **8** (12 mg) (Zheng et al., 2008), Artonin A **9** (23 mg) (Hano et al., 1989; Chung et al., 1995), Cycloartobiloxanthone **10** (23 mg) (Uvais et al., 1989), Artobiloxanthone **11** (11 mg) (Uvais et al., 1989), Artoindonesianin A-3 **12** (9 mg) (Syah et al., 2006) Artonol B **13** (12 mg) (Aida et al., 1997). The (25.5 g) was also fractionated on a silica gel (100-200 mesh) column to afford eight fractions (Fr.ALA.1-Fr.ALA.20). Fraction Fr.ALA.3-20 were chromatographed over silica gel to give another four compounds; 4-Prenyl oxyresveratrol **3** (3 mg) (Takasugi et al., 1978), Moracin S **14** (2.5 mg) (Kapche et al., 2009) including *E*-resveratrol (1) and Oxyresveratrol **(2)**. Oxyresveratrol **(2, 16)**, 46 g) was precipitated out from the heartwood of *A. lakoocha* acetone extract (65 g) without any column chromatographic separations. Structures of isolated compounds were confirmed by various spectroscopic analyses and also compared with the available literature data (See supporting information). Structure of isolates are shown in fig.1.

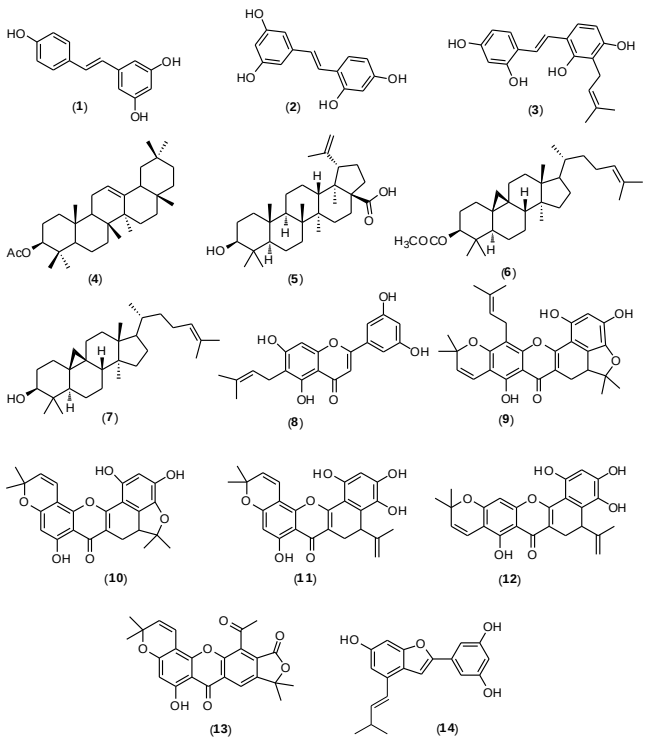

Figure 1: Structure of isolated compounds from *A. camansi* and *A. lakoocha*

Biological screening of isolated compounds

In order to showcase the biological activity of isolated compounds, we examined the hypoglycaemic properties in terms of α-glucosidase, α-amylase, antiglycation and glucose uptake. Except triterpenoids and moracin S, all the tested compounds showed a moderate

α-glucosidase inhibition compared to acarbose. In particular, oxyresveratrol (**3**), artobiloxanthone (**11**) and artoindonesianin A-3 (**12**) showed prominent α-glucosidase inhibitory activity with IC_{50} values of 37.38 ± 1.11, 53.74 ± 0.76 and 54.04 ± 0.40 µM, respectively. α-Glucosidase inhibitory activity of *E*-resveratrol (**1**) was described in our previous paper (Sasikumar et al., 2019). The results also showed that artobiloxanthone (**11**) inhibited α-amylase (IC_{50} 19.69 ± 0.06 µM) which was comparable with that of standard, acarbose (IC_{50} 8.99 ± 0.48 µM). AGEs are reported to be associated with complications due to prolonged diabetes (Singh et al., 2001). From our study, it is evident that artocarpesin (**8**) and artonol B (**13**) possessed prominent antiglycation activity (IC_{50} 50.10 ± 0.25 and 94.77 ± 0.53 µM, respectively) (Table 2).

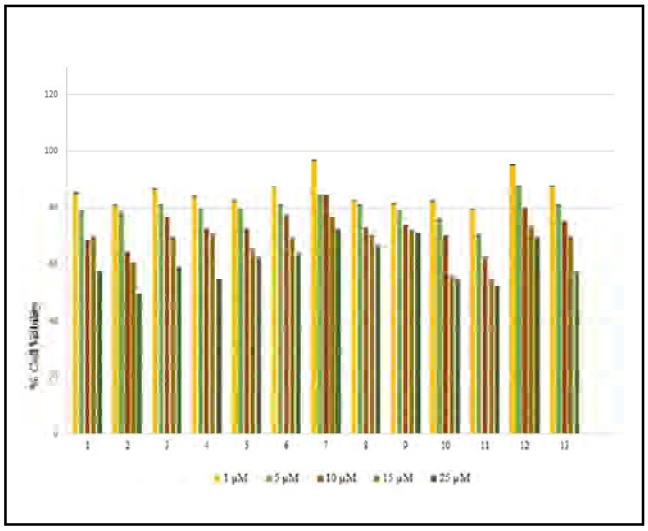

Figure 2: MTT cytotoxicity assay of isolated compounds. L6 myoblasts were treated with various concentrations of compounds (0, 1, 5, 10, 15, 25 µM) for 24 h and cytotoxicity was determined by MTT assay. All data are represented as means ± SD (n=3)

Table 2: Antidiabetic activity of isolated compounds

Compound	α - glucosidase (µM)	α- amylase (µM)	Antiglycation (µM)
Oxyresveratrol (**2**)	37.38 ± 1.11	2363.34 ± 0.08	232.15 ± 0.53
4-Prenyl oxyresveratrol(**3**)	62.00 ± 0.45	789.50 ± 0.08	917.58 ± 0.98
β-Amyrin acetate (**4**)	61.51 ± 0 .84	215.33 ± 0.44	180.02 ± 0.58
Betulinic acid (**5**)	328.25 ± 0.55	136.25 ± 0.17	128.86 ± 0.37
Cycloartenol acetate (**6**)	296.25 ± 0.05	104.28 ± 0.06	195.42 ± 0.23
Cycloartenol (**7**)	218.25 ± 0.42	221.22 ± 0.76	120.78 ± 0.28
Artocarpesin (**8**)	67.66 ± 0.30	537.50 ± 0.26	50.10 ± 0.25
Artonin A (**9**)	142.24 ± 1.03	144.24 ± 0.58	118.55 ± 0.36
Cycloartobiloxanthone (**10**)	63.64 ± 0.31	29.00 ± 0.05	103.43 ± 0.50
Artobiloxanthone (**11**)	53.74 ± 0.76	19.69 ± 0.06	179.78 ± 0.06
Artoindonesianin A-3 (**12**)	54.04 ± 0.40	25.93 ± 0.65	191.05 ± 0.53
Artonol B (**13**)	65.66 ± 0.31	139.86 ± 0.93	94.77 ± 0.53
Moracin S (**14**)	418.25 ± 0.11	286.31 ± 0.76	618.25 ± 0.12
Acarbose	52.87 ± 0.22	8.99 ± 0.48	…….
Ascorbic acid	…….	…….	154.63 ± 0.49

All data are represented as mean ± standard deviation (n=3)

MTT assay

To fix the safe dose range for glucose uptake, the cytotoxicity of the compounds were measured at different concentrations (0, 1, 5, 10, 15 and 25 µM) by means of MTT assay for 24 hours. All the tested compounds were found to be less toxic in a dose dependent manner (<20 %) even at 5 µM concentration (Fig. 2).

2-NBDG uptake assay by fluorescent microscopy

Glucose uptake was monitor using fluorescent tagged deoxy-glucose analogue 2-NBDG. In the present study, the L6 rat myotubes were challenged with isolated compounds at 5 µM concentration for 24 hours. Among them *E*-resveratrol (**1**), artobiloxanthone (**11**) and artonol B (**13**) exhibited optimum glucose uptake (Fig. 3. showing high intense fluorescence) which is comparable to the

standard metformin (100 µM). The fluorescent intensity of the images was analysed using BD Image Data Explorer software.

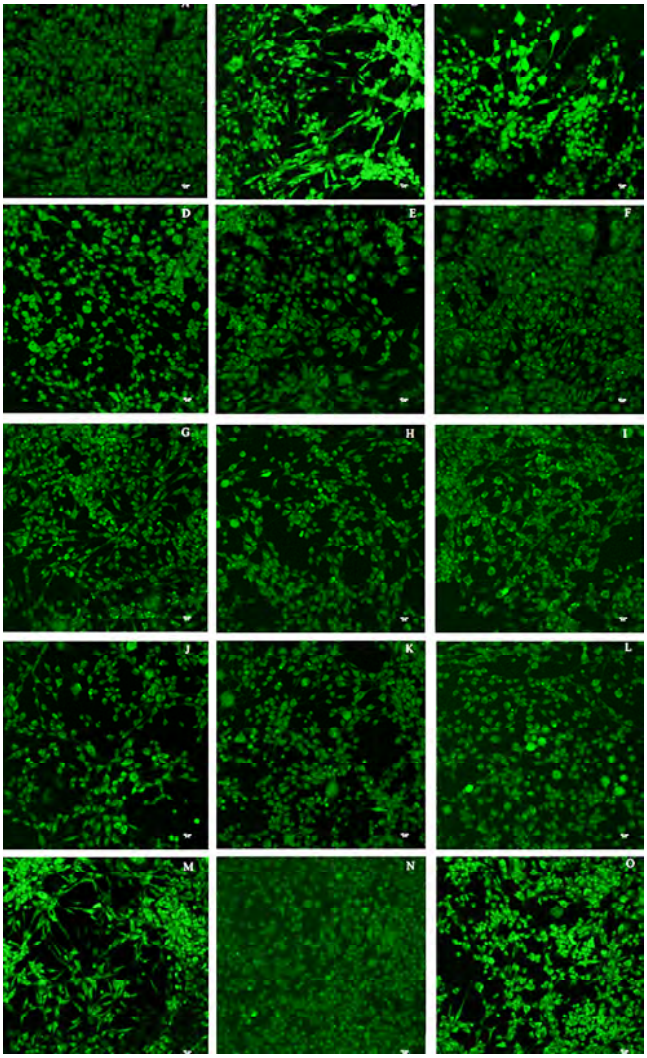

Figure 3: 2-NBDG uptake assay by fluorescent microscopy in L6 rat myotubes: (A) untreated cells, (B) 100 µM metformin (C) *E*-resveratrol (1, D) oxyresveratrol. (2, E) 4-prenyl oxyresveratrol, (3, F) α-amyrin acetate, (4, G) betulinic acid, (5, H) cycloartenol acetate, (6, I) cycloartenol, (7, J) artocarpesin, (8, K) artonin A, (9, L) cycloartobiloxanthone, (10, M) artobiloxanthone, (11, N) artoindonesianin A-3, (12, O) artonol B (13), all data are represented as means ± SD (n=3)

2-NBDG analysis by Flow cytometry

Flow cytometry accomplished quantitative measurement of 2-NBDG within the cells. Flow cytometry analysis shown out 15.9 % uptake in control and 35.7% in metformin at 100 µM concentration. Based on the results obtained in 2-NBDG uptake assay by fluorescent microscopy, we selected *E*-resveratrol **(1)**, artobiloxanthone **(11)**, and artonol B **(13)** for the quantitative measurement of 2-NBDG uptake. The compounds at 5 µM concentration showed significant increase in 2-NBDG uptake which is comparable with the positive drug control. *E*-Resveratrol **(1)** showed 32.2 % uptake, while artobiloxanthone **(11)** and artonol B **(13)** showed 32.9 % and 33.5 % uptake respectively (Fig.4). Thus, the compounds were found to induce 2-NBDG uptake of cells by enhancing their fluorescence intensities in L6 myotubes.

In our previous study, we discussed the glucose uptake potential of resveratrol oligomers isolated from rare plants from Vitaceae and Dipterocarpaceae family. Result depict that resveratrol trimer α-viniferin and tetramers (+) and (-)-hopeaphenol showed glucose uptake of 49.6 %, 31 % and 26.4 % at 75 and 100 µM (Sasikumar et al., 2016, 2019). In the present study, we spotted a significant increase in glucose uptake in L6 myotubes on pretreatment of compounds at 5 µM concentrations which was comparable to that of the antidiabetic drug, metformin (100 µM). This is the first report of antidiabetic screening of isolated compounds from *Artocarpus camansi* and *Artocarpus lakoocha* inducing glucose uptake in muscle cells presenting a potential antidiabetic target by improving insulin sensitivity.

CONCLUSION

In the present study, we have isolated and structurally characterized **14** compounds from the stem bark of *A. camansi* and *A. lakoocha*. From best of our knowledge, we are reporting the compounds (**3**, **8**, **9**, **10**, **11**, **12** and **13)** and their antidiabetic activity for the first time from these species. In particular, oxyresveratrol **(2)**, displayed prominent IC_{50} value of 37.38 ± 1.11 µM in α-glucosidase inhibitory assay. Glucose uptake was performed by 2-NBDG in L6 muscle cells using flow cytometry. It is also interesting to observe that *E*-resveratrol **(1)** (32.2 %), artobiloxanthone **(11)** (32.9 %) and artonol B **(13)** (33.5 %) significantly increased glucose uptake in L6 cells. These multiple modes of action increase the interest in the use of tested compounds as a therapeutic intervention for diabetes.

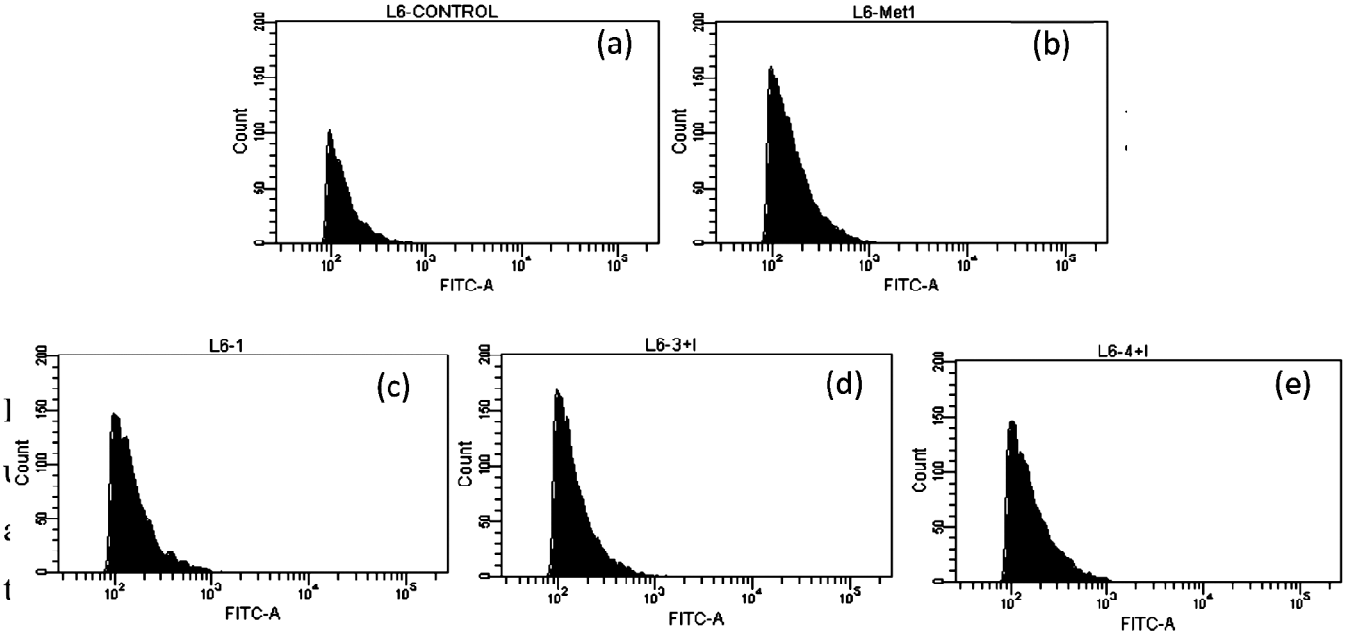

Figure 4: 2-NBDG assay by flow cytometry in L6 rat myoblast cells: FITC histograms in (a) untreated cells (15.9%); (b) 100 µM metformin (35.7%); (c) *E*-resveratrol (1,32.2%); (d) artobiloxanthone (1,32.9%); (e) artonol B (13,33.5%); Data are representative histograms from three independent experiments

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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