Mechanisms and Antidiabetic Compounds of *Balanites Aegyptiaca Delile* Plant: A Review

Abstract

Balanites aegyptiaca has been reported to exert significant antidiabetic activity. It was reported to have lowered blood glucose levels by different mechanisms where various active compounds were identified. In this review, bioactive compounds and likely mechanisms of action were highlighted. The review showed that different mechanisms such as oxygen radical scavenging activity, increased insulin secretion, and enhanced regeneration of beta cell of the pancreas were reported to explain antidiabetic effect of the plant. The plant also exerted alpha amylase inhibitory activity, insulinomimetic effect and enhanced glucose uptake by tissues. Compounds like saponins, simple phenolics and flavonoids are the likely active molecules reported. In conclusion, *Balanites aegyptiaca* has potential chemicals which exerted different antidiabetic mechanisms and if properly harnessed might lead to the discovering of new substance which could better serve in the management of diabetes mellitus.

Keywords: Balanites aegyptiaca, antidiabetic, active compounds, mechanisms

1.0 INTRODUCTION:

Balanites aegpytiaca Delile is known as 'Desert date or Thorn tree' in English, is a member of *Zygophyllaceae*, one of the most common plant species of the dry land areas of Africa and South Asia [1,2]. In Nigeria, it is found mostly in the Northern region. It is known as '*Aduwa*' in Hausa, '*Utazi'* in Igbo, and '*Teji'* in Yoruba. It grows up to 6 -10 meters in height, is highly resistant to stresses such as sandstorms and heat waves, and grows with minimal available moisture.

The plant (*Balanites aegpytiaca Delile)* has long history of traditional uses for wide ranges of disease [3]. For instance, the kernel oil is used for the treatment of wounds in Nigeria [4]. Also, in Nigeria, a mixture of dried leaves powder of *Balanites aegpytiaca Delile* and *Ricinus communis* in water is used for contraception [5]. In the north-eastern part of Nigeria, the fruit-mesocarp is prepared as pap and taken as remedy against symptoms of diabetes mellitus and other related diseases (personal communication). In Egyptian folk medicine, the fruit is used as an oral hypoglycemic [6]. Aqueous extract of the fruit mesocarp is used in Sudanese folk medicine in the treatment of jaundice [7]. The bark, fruits, seeds and leaves of *Balanites aegpytiaca Delile* are widely used in folk medicine [3,8].

Balanites aegyptiaca extracts has been reported to exert antihyperglycemic activity in both diabetic mice and rats [9, 10]. The fruit and seed extracts of *Balanites aegyptiaca* has been widely studied and were reported to have exhibited prominent antihyperglycemic activity and also improved lipid profile toward normal levels in diabetic-induced animals [11,12,13]. *Balanites aegyptiaca* fruit extract was reported to have stimulated insulin secretion [11, 14], inhibited intestinal α-amylase activity [15], and increased muscle basal glucose uptake [10] to lowered blood glucose level. The seed extract was reported to have exerted antihyperglycemic effect by ameliorating beta-cell dysfunction [13] while Shafik *et al* [16] suggested antioxidant activity. In a recent studies, it was reported that the leaf extract stimulated erythrocytes glucose uptake in

type II diabetic patients [17] while Gawade and Farooqui [18] reported that it inhibited alpha amylase activity *in vitro*.

The phytochemical investigations of various parts of *Balanites aegyptiaca* extracts showed that the plant is rich with some biologically active compounds like flavonoids, phenolics, terpenes, tanins and saponins [19, 20, 21]. Literature reported compounds like coumarins and quercetins in the leaves, alkaloids and coumarins in the stem-bark while rutins in the fruit and seed kernel among others [7, 16, 22]. Some antidiabetic bioactive compounds that were reported are saponins [6, 12], phenolic compounds like vanillic and syringic acids as well as flavonoids (rutin) and isorhamnetin in fruit [10, 20] while Shafik *et al* [16] reported isorhamnetin, rutinoside, aglycone-quercetin from the plant seed extract.

The variety of chemicals possess by *Balanites aegyptiaca* might have attributed to the different mechanisms exerted to low blood glucose in diabetic subjects and could be of potential for discovering of new chemical that might serve in the management of diabetes mellitus. In this review, antidiabetic bioactive compounds and mechanisms of action of *Balanites aegyptiaca* plant were highlighted with the aim to portray their potential for pharmaceutical consideration.

2.0 ANTIDIABETIC ACTIVITY OF VARIOUS PARTS OF *BALANITES AEGPYTIACA*

Balanites aegpytiaca play an important role in the management of diabetes mellitus. The antihyperglycemic effects of its various parts has been studied in several diabetic animals model [9, 10, 23]. The extracts of the fruit-mesocarps of *Balanites aegpytiaca* was the most widely studied and was reported to exhibited potential antihyperglycemic activity and also improved diabetic complication toward normal in the diabetic-induced animals [11, 12 ,13, 20].

Kamel *et al* [6] had earlier reported that aqueous extract of the fruit mesocarp, as well as the polysaccharide fraction (precipitated by excess of alcohol) and the supernatant (saponin-rich), exerted significant antidiabetic activities in STZ-induced diabetic mice. Samir *et al* [11] reported antidiabetic and antilipidemic effects of water and ethanolic extracts of the *Balanites aegyptiaca* fruits in normal senile diabetic rats. The *Balanites aegyptiaca* fruit extract was reported to have

reduced blood glucose level by 24 % in STZ-induced diabetic rats [10]. Motaal *et al* [15] has reported potential antidiabetic activities of different extracts and fractions of the *Balanites aegyptiaca* fruit in cultured C2C12 skeletal muscle cells and 3T3-L1 adipocytes.

The aqueous extract of *Balanites aegpytiaca* seeds has been reported to exert hypoglycemic and hypolipidemic effects, the study showed that it increased insulin level, and decreased insulin resistance [13]. The antihyperglycemic effect of *Balanites aegyptiaca* seed kernel was reported in alloxan-induced diabetic rats [16, 23].

Pharmacognostic studies on the effectiveness of *Balanites aegpytiaca* leaves and stem-bark extracts showed that they can be used in the treating or prevention of diseases [24, 25]. In regard to this, literature survey on the use of *Balanites aegyptiaca* leaf and stem-bark for treatment of various ailment was conducted and found that several studies has reported their antimicrobial activities [26,27, 28]. The leaf extract has also be reported to have improved liver parameters in rats [29]. The leaves and stem-bark were recently reported as the potential parts of *Balanites aegyptiaca* use by traditional medicine practitioners for the management of diabetes mellitus in Zaria, Kaduna State, Nigeria [8]. In addition, recent studies on the *Balanites aegyptiaca* leaf extracts reported that it possess antidiabetic properties [17, 18]. The review found that the *Balanites aegyptiaca* fruit was the most widely studied for antidiabetes, followed by the seed whereas very few data reported on *in vivo* antidiabetic investigation of the plant leaf and the stem-bark based on the figures presented in Table 1.

3.0 SOME BIOACTIVE COMPOUNDS OF *BALANITES AEGYPTIACA*

Phytochemical investigation of various parts of *Balanites aegpytiaca* has revealed that it contained a variety of compounds like coumarins and quercetins in the leaves, alkaloids and coumarins in the stem-bark while rutins was in the fruit among others [7, 10, 21, 22]. In general, phytochemicals like flavonoids, phenols, saponins, phytosterols, terpenes and alkaloids were reported from the various parts of *Balanites aegyptiaca* [19, 20, 21].

The antidiabetic bioactive compounds reported are saponins [6, 12]. Motaal *et al* [10] has reported rutin and isorhamnetin while Al-Malki *et al* [20] reported two phenolics; vanillic and syringic from the fruit-mesocarp extract. Shafik *et al* [16] has reported some flavonols in the seed kernel of this plant. Phenolic compounds like eugenol and isoeugenol has been identified in the leaf extract of the *Balanites aegyptiaca* [30]. These phenolics; eugenol and isoeugenol has been identified in several medicinal plants [31, 32], and were reported to have exerted antioxidant, anti-inflammation, anticancer, antidiabetic activity [33, 34, 35].

Specifically, eugenol isolated from Clove plant has been reported to exert antidiabetic activity by influencing the activities of enzymes involved in glucose metabolism [36, 37]. Another study also reported that eugenol isolated from *Ocimum gratissimum* leaves inhibited alpha-glucosidase activity to exhibit antidiabetic effect [35]. Study by Kim *et al* [38] has reported that isoeugenol increased glucose uptake in skeletal muscle. A recent study has reported phenol, 2, 4-bis (1, 1-dimethyethyl), neophytadiene, 3, 7, 11,15-tetramethyl-[R-[R*,R*-(E)]-(T-phytol) in the leaf extract of *Balanites aegyptiaca* [18].

4.0 ANTIDIABETIC MECHANISMS OF *BALANITES AEGYPTIACA*

Studies have shown that *Balanites aegyptiaca* exert antidiabetes, antioxidant, antilipidemia etc. Different variety of biologically active chemicals possess by the plant [7,10,22] could have attributed to its different biological functions. In general, It was reported that the hypoglycemic activities of medicinal plants mainly attributed to reduce intestinal absorption of dietary carbohydrate, modulation of the enzymes involved in glucose metabolism, improvement of β-cell function and insulin action, stimulation of insulin secretion, antioxidant and anti-inflammatory [39,40]. *Balanites aegyptiaca* seem to act by more than one mechanisms to low blood glucose. The plant showed to have oxygen radical scavenging activity, increase insulin secretion, enhanced regeneration of beta cell of the pancreas. It also possess alpha amylase inhibitory activity, insulinomimetic effect and enhanced glucose uptake by tissues.

According to Al-Malki *et al* [20] and Shafik *et al* [16], *Balanites aegptiaca* extract exert antioxidant activity to combat diabetes mellitus. The likely *Balanites aegyptiaca* compounds that exerted oxygen radical scavenging activity are vallinic, syringic and β-sitosterol, isorhamnetin 3-rutinoside, 3-robinobioside, 3-0-glucoside, 3-0-galactoside, 3,7-diglucoside, quercetin-3-glucoside and aglycones quercetin as reported by Al-Malki *et al* [20] and Shafik *et al* [16]. It has been reported that isorhamnetin from plant ameliorate hyperglycemia and oxidative stress [41]. A study have suggested that isorhamnetin glycosides may possess the antidiabetic effect and their influence on lipid content, endoplasmic reticulum stress markers and the expression of enzymes regulating lipid metabolism [42]. Rutin have been shown to stimulate glucose uptake in the rat soleus muscle via the PI3K, a typical protein kinase C and mitogen-activated protein kinase pathways [43]. Rutin has been reported to significantly improved body weight, reduced plasma glucose and restored the depleted liver antioxidant status and serum lipid profile in HFD/STZ induced diabetic rats [44].

Balanites aegyptiaca extract was reported to have stimulated insulin secretion to lowered blood glucose levels [11, 14]. Samir *et al* [11] has reported that oral administration of both aqueous and ethanolic extract of *Balanites aegyptiaca* significantly increased serum insulin levels in diabetic treated rats. In another study on STZ-induced diabetic rats, it was reported that the antihyperglycemic effect of the plant fruit was mediated through insulin mimetic effect and inhibition of intestinal α-amylase activity [15]. It was reported that the activity of some glucose metabolic enzymes like glucose-6-phosphatase was markedly decreased whereas hexokinase was increased upon administration of the plant extract [15, 16]. In a same study, the plant extract was reported to have inhibited α-amylase activity in dose-dependent manner [15].

Motaal *et al* [10] reported that *Balanites aegyptiaca* extract increased muscle basal glucose uptake. Motaal *et al* [10] stated that the increased muscle basal glucose uptake participated in the traditionally known, and *in vivo* proven, antidiabetic effect of the *Balanites aegpytiaca*. The study suggested that phenolic compounds might have attributed to this activity. In an i*n vitro* studies, it was reported that plant polyphenols such as quercetin, resveratrol improved insulin-

dependent glucose uptake in muscle cells and adipocytes by translocation of glucose transporter, GLUT4, to plasma membrane mainly through induction of the AMP-activated protein kinase (AMPK) pathway [45, 46](Park et al., 2007; Zhang et al., 2011).

Another study reported that *Balanites aegyptiaca* extract was able to ameliorate beta-cell dysfunction [13]. According to Mahdy *et al* [17], *Balanites aegyptiaca* leaf extract in a recent study was able to stimulated erythrocytes glucose uptake in type II diabetic patients while Gawade and Farooqui [18] in an *in vitro* study has reported that it inhibited alpha amylase activity. Some of the *Balanites aegyptiaca* compounds with antidiabetic properties and likely mode of actions is summarized in Table 2..

5.0 **CONCLUSION**

This review provide information on antidiabetic potential of the medicinal plant '*Balanites aegyptiaca*. It harmonizes the findings that reported different mechanisms exerted by the plant and the likely active compounds for easy assimilation. The plant seems to contain a variety of chemicals like saponins, simple phenolics and flavonoids which act to reduce blood glucose levels by either oxygen radical scavenging activity, increase insulin secretion, enhanced regeneration of beta cell of the pancreas. It also exert alpha amylase inhibitory activity, insulinomimetic effect and enhanced glucose uptake by tissues. Proper harnessing of these compounds could lead to the discovering of new substance that would better serve in the management of diabetes mellitus.

Table 1. Balanites aegyptiaca Parts with Antidiabetic Activity Based on Published Articles Report

S No.	Plant Parts	Part Used Based on Article	Frequency of Part Used	Percent Frequency
1	Fruit	[6,10, 11, 12, 14,15, 20,47]	8	57.14
2	Seeds	[13, 16, 23]	3	21.43
3	Leaf	[17,18, 30]	3	21.43

NB: Numbers in bracket represent article that reported antidiabetic effect of the plant part

Table 2. *Balanites aegyptiaca Del*. Antidiabetic Bioactive Compounds and Mode of Actions

Plant Parts	Type of Extract	Bioactive Compounds	Mode of Action	Reference
Fruit- mesocarp and epicarp	Aqueous and ethanolic extracts	Steroidal saponins, Isorhamnetin-3-0-robinobioside, Isorham-netin-3-0-rutinoside	--	[6]
Fruit flesh	Aqueous and ethanolic extracts	--	Stimulation of insulin secretion	[11]
Fruit	Saponin rich-extract	Saponins	--	[12]
Fruit-mesocarp	Aqueous extract	--	Insulinomimetic effect and inhibition of alpha amylase activity	[15]
Fruit-mesocarp	Ethyl acetate and dichloromethane extracts	Rutin and isorhamnetin	Enhanced muscle basal glucose uptake	[10]
Seed	Aqueous extract	--	Amelioration of β–cell dysfunction	[13]
Seed Kernel	Kernel cake	--	--	[23]
Fruit	--	Trigonelline	--	[47]
Fruit-mesocarp	Ethyl acetate extract	Vallinic, syringic and β-sitosterol	Antixoidant activity	[20]
Seed Kernel	Ethanolic extract	Isorhamnetin 3-rutino-side, 3-robinobioside, 3-0-glucoside, 3-0-galacto-side, 3,7-diglucoside, quercetin-3-glucoside, aglycones quercetin	Antioxidant activity	[16]
Fruit-pericarp	Methanolic extract	Furostanol saponin	Stimulation of insulin secretion	[14]
Leaves	--	--	Stimulation of erythrocyte glucose uptake	[17]
Leaves	Ethanolic-aqueous fraction	Eugenol, isoeugenol, etc	--	[30]
Leaves	Ethanolic extract	Phenol, 2,4-bis(1,1-dimethy ethyl), neophy-tadiene, 3,7, 11,15-tetra methyl-[R-[R*, R*-(E)]-(T-phytol)	Inhibition of alpha amylase activity	[18]

-- = not specified

References

1. Hall JB and Waljer DH. *Balanies aegyptiaca* Del. A Monograph School of Agricultural and Forest Science. Banger: University of Wales, 1991:1-2.
2. Hall JB. Ecology of a key African multipurpose tree species *Balanites aegyptiaca* Del. The state of knowledge. *Forest Ecological Management*. 1992; 50: 1-30.
3. Chothani LD and Vaghasiya HU. A review on *Balanites aegyptiaca* Del (desert date): phytochemical constituents, traditional uses, and pharmacological activity. *Pharmacogen res*erve. 2011; 5(9): 55-62.
4. Breyer JM and Brandwijk MG. The medicinal and poisonus plants of Southern and Eastern Africa 2nd ed. London: Livingstone; 1982, Pp. 1064–1065.
5. Oliver-Bever B. Medicinal plants in tropical West Africa. Cambridge: Cambridge University Press. 1986; 54 Pp., 184–185.
6. Kamel MS.Studies on *Balanites aegyptiaca* fruit, an antidiabetic Eygptiaca folk medicine. *Chemical and Pharmaceu*tical Bulletin. 1991; 39: 1229-1233
7. Sarker SD, Bartholomew B and Nash RJ. Alkaloids from *Balanite aegyptiaca*. *Fitoterapia*. 2000; 71:328–330.
8. Abubakar US, Adbullahi S, Ayuba V, Kaigama S, Halidu US, and Ayuba MK. Medicinal plants used for the management of diabetes mellitus in Zaria, Kaduna State, Nigeria. Journal of Pharmacy and Pharmacognosy research. 2017; 5(3):156-164.
9. Mansour HA, and Newairy AA. Amelioration of impaired renal function associated with diabetes mellitus by *Balanites aegyptiaca* fruits in streptozotocin-induced diabetic rats. *Journal of Medical Research Inst*. 2000; 21:115-125.
10. Motaal A A, Shaker S and Haddad PS. Antidiabetic Activity of Standardized Extract of *Balanites aegyptiaca* Fruits using Cell-based Bioassays. *Parmacognosy Journal*. 2012; 4(30): 20-24.
11. Samir AM, Zaahkouk S, Rashid ZA and Mattar AF. Anti – diabetic properties of water and ethanolic extract of *Balanites aegyptiaca* fruits flesh in senile diabetic rats. *Egyptian Journal of Hospital Medicine*. 2003; 10: 90-108.
12. George DH, Ali HK and El-Abbas OA. Evaluation of the biological activity of *Balanites aegyptiaca* Del Saponin in the control of type 11 diabetes mellitus mellitus on rats and the growth of Escherichia coli. *Ahfad Journal of Women Change. 2006; 23*: 2. Abstract
13. Eman Helal GE, Abd El-Wahab SM, El Refaey H and Mohammad AA. Antidiabetic and antihyperlipidemic effect of *Balanites aegyptiaca* Seeds (Aqueous Extract) on diabetic rats. *The Egyptian Journal of Hospital Medicine*. 2013; 52: 725–739.
14. Ezzat SM, Abdel Motaal A, El-Awdan SAW. *In vitro* and *in vivo* antidiabetic potential of extract and a furostanol saponin from *Balanites aegyptiaca*. *Pharmaceutical Biology*. 2017; 55(1): 1931-1936.
15. Gad MZ, El-Sawalhi MM, Ismail MF and El-Tanbouly ND. Biochemical study of the anti-diabetic action of the Egyptian plants *Fenugreek* and *Balanites*. *Molecular and Cellular Biochemistry*. 2006; 281: 173–183.
16. Shafik NH, Shafek RZ, Michael HN and Eskander EF. Phytochemical study and antihyperglycemic effects of *Balanites aegyptiaca* kernel extract on alloxan induced diabetic male rats. *Journal of Chemistry and Pharmacy Research*. 2016; 8(3):128-136.
17. Mahdy E, El-Sayed M. Antidiabetic effect of *Balanites aegyptiaca* leaves extract by regulation of erythrocyte glucose uptake in diabetic patient type 2 *in vitro, Egyptian Journal of Hospital Medicine. 2017;* 67(2): 525-535.
18. Gawade B and Farooqui M. Investigation of phytochemical and alpha amylase inhibition activity of *Balanites aegyptiaca* leaves. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2018; 9(1):459-464.
19. Qusti SY, Sharahili RY and Moselhy SS . Role of Balanites aegyptiaca in Attenuation of Diabetic Nephropathy. *International Journal of life Sciences Re*search. 2015; 3(4): 8-14.

20. Al-Malki AL, Barbour EK, Abullnaja KO, and Moselhy SS. Management of hyperglycemia by ethyl acetate extract of Balanites aegyptiaca (Desert Date). *Molecules*. 2015; 20 (8):14425-14434.
21. Gidey T. K. Isolation and structure elucidation of flavonoids from leaves extract of *Balanites aegyptiaca delile*. *International journal of modern chemistry and applied science*. 2016; 3(3):446-449.
22. Salwa AM and El Hadidi MN. Flavonoids of *Balanites aegyptiaca* (*Balanitaceae*) from Egypt. *Plant System Evolution.1988;* 160(3):153–158.
23. Nadro MS and Samson FP. The effects of *Balanites aegyptiaca* kernel cake as supplement on alloxan -induced diabetes mellitus in rat. *Journal of Applied Pharmaceutical Science*. 2014; 4 (10): 058-061.
24. Gupta SC, Shenoy S and Kotecha M. Pharmacognostical and phytochemical evaluation of Balanites aegyptiaca Del stem-bark. *Journal of Pharmacy*. 2012; 3(7):169:173.
25. Salve KM. Pharmacognostic effectives of *Balanites aegyptiaca (L) Delile*. International *Journal of Research in Biosciences, Agriculture and Technology*. 2016; 4(1): 165-167.
26. Doughari JH, Pukuma MS and De N. Antibacterial effects of *Balanites aegyptiaca (L) Del.* and *oleifera Lam* on. *Salmonella typhi African Journal of Biotechnology*. 2017; 6(19):2212-2215.
27. Hena JS, Adamu AK, Iortsuun DN and Olonitola S. Phytochemical screening and antimicrobial effect of the aqueous and methanolic extracts of root of *Balanites aegyptiaca (Del)* on some bacterial species. *Science World Journal*. 2010; 5(2):59-62.
28. Abdulhamid A and Sani I. Preliminary phytochemical screening and antimicrobial activity of aqueous and methanolic leave extracts of Balanites aegyptiaca (L). *International research Journal of Pharmaceutical and Biosciences*. 2016; 3(1):1-7.
29. Jacob A, Shahu BB and Orendu AM. Effects of methanolic leaves extract of *Balanites aegyptiaca del.* on some biochemical parameters in wistar strain albino rats. Nova journal of Medical and Biological Sciences. 2017; 4(2016).
30. Hassan DM, Anigo KM, Umar IA, Alegbejo JO. Evaluation of Phytoconstituent of *Balanites aegyptiaca* (L) Del Leaves and Fruit Mesocarp. MOJ Bioorganic & Organic Chemistry. 2017; 1(6):1-4.
31. Purwantiningsih, Hussin, A.H., and Chan, K.L. Free Radical Scavenging Activity of the Standardized Ethanolic Extract of *Eurycoma Longifolia* (Taf-273). *International Journal of Pharmacy and Pharmaceutical Science. 2011;* 3(4): 343-347.
32. Dandekar, R., Fegade, B., and Bhaskar, V.H. GC-MS analysis of phytoconstituents in alcohol extract of *Epiphyllum oxypetalum* leaves. *Journal of Pharmacy and Phytochemistry*. 2015; 4(1): 149-154.
33. Jeong, J.B., and Jeong, H.J. 2-Methoxy-4-vinylphenol can induce cell cycle arrest by blocking the hyper-phosphorylation of retinoblastoma protein in benzo[a]pyrene-treated NIH3T3 cells. *Biochemistry Biophysics Research Community*.2000; 400(4): 752-757.
34. Suttiarporn, P., Sookwong, P., and Mahatheeranont, S. Fractionation and Identification of Antioxidant Compounds from Bran of Thai Black Rice cv. Rice berry, *International Journal of Chemical Engineering and Applications*. 2015; 7(2):109-114.
35. Singh, P., Jayaramaiah, H.R., Agawane, S.B., Vannuruswamy, G., Korwar, A.M., Anand, A. Potential Dual Role of Eugenol in Inhibiting Advanced Glycation End Products in Diabetes mellitus: Proteomic and Mechanistic Insights. *Scientific Report. 2016;* 6, 18798. doi: 10.1038/srep18798.
36. Srinivasan, S., Sathish, G., Jayanthi, M., Jayanthi, M., Muthukumaran, J, Muruganathan, J. Ameliorating effect of *eugenol* on hyperglycemia by attenuating the key enzymes of glucose metabolism in streptozotocin-induced diabetic rats. *Molecular and Cellular Biochemistry*. 2014; 385(1-2): 159-168.

37. Jeong, K.J., Kim, D.Y., Quan, H.Y., Jo, H.K., Kim, G.W., and Chung, S.H. Effects of eugenol on hepatic glucose production and AMPK signaling pathway in hepatocytes and C57BL/6J mic. *Fitoterapia*. 2014; 93:150–162. doi: 10.1016/j.fitote.2013.12.023.
38. Kim, N., Lee, J.K., Lee, H.J., Lee, Y.W., Kim, H.P., Kim, S.K. AMPK, a metabolic sensor, is involved in isoeugenol-induced glucose uptake in muscle cells. *Journal of Endocrinology*. 2016; 228(2): 105–114.
39. Prince PSM and Kannan N K. Rutin improves glucose homeostasis in streptozotocin diabetic tissues by altering glycolytic and gluconeogenic enzymes. *Journal of Biochemistry and Molecular Toxicology*. 2006; 20(2):96-102.
40. Bahadoran Z, Mirmiran P and Azizi F . Dietary polyphenols as potential nutraceuticals in management of diabetes mellitus: a review. *Journal of diabetes mellitus and Metabolic Disorders*. 2013; 12:43. doi 10.1186/2251-6581-12-43-52.
41. Yokozawa T, Kim HY, Cho EJ, Choi JS, Chung HY. Antioxidant effects of isorhamnetin 3,7-di-O-beta-D-glucopyranoside isolated from mustard leaf (*Brassica juncea*) in rats with streptozotocin-induced diabetes. J Agric Food Chemistry. 2002; 50:5490–5495.
42. Rodríguez-Rodríguez C, Torres N, Gutiérrez-Uribe JA, Noriega LG, Torre-Villalvazo I, Leal-Díaz AM, et al. The effect of isorhamnetin glycosides extracted from *Opuntia ficus-indica* in a mouse model of diet induced obesity. Food Function. 2015; 6:805–815.
43. Kappel VD, Cazarolli LH, Pereira DF, Postal BG, Zamoner A, Reginatto FH, et al. Involvement of GLUT-4 in the stimulatory effect of rutin on glucose uptake in rat soleus muscle. Journal Pharm Pharmacol.2013; 65:1179–1186.
44. Niture NT, Ansari AA, Naik SR. Anti-hyperglycemic activity of rutin in streptozotocin-induced diabetic rats: an effect mediated through cytokines, antioxidants and lipid biomarkers. Indian J Exp Biol. 2014; 52:720–7.
45. Park, C.E., Kim, M.J., Lee, J.H., Min, B.I., Bae, H., Choe, W. Resveratrol stimulates glucose transport in C2C12 myotubes by activating AMP-activated protein kinase. 2007; 39(2): 222-229.
46. Zhang, B., Kang, M., Xie, Q., Xu, B., Sun, C., Chen, K. Anthocyanins from Chinese bayberry extract protect cells from oxidative stress- mediated injury via HO-1 upregulation. *Journal of Agriculture and Food Chemistry*. 2011; 59(2): 537-545.
47. Farag M A and Wessjohann LA. Unravelling the active hypoglycemic agent trigonelline in *Balanites aegyptiaca* date fruit using metabolite fingerprinting by NMR. *Journal of Pharmaceutical and Biomedical Analysis*. 2015; 115: 383-387.