Mechanisms and Antidiabetic Compounds of *Balanites Aegyptiaca Delile* Plant: A mini-review

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Abstract

Balanites aegyptiaca has been reported to exert significant antidiabetic activity. It was reported to 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 was 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 steroidal 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

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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 grow 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]. 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 for 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 have 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*.

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Phytochemical investigations of the various parts of *Balanites aegyptiaca* extracts showed that the plant is rich with some biologically active compounds like flavonoids, phenolics, terpenes, tanins and steroidal 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 steroidal 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 the new chemical that might better 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 plays an important role in the management of diabetes mellitus. The antihyperglycemic effects of its various parts have 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 reported to exhibited potential antihyperglycemic activity, and was also reported 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 an 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

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et al. [15] have 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 increases insulin level, and decrease insulin resistance [13]. The antihyperglycemic effect of *Balanites aegyptiaca* seed kernel has been 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 conducted showed that several studies have 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]. This review found that *Balanites aegyptiaca* fruit was the most widely studied for antidiabetes, followed by the seed whereas very few data reported antidiabetic investigations 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. It was earlier reported that the leaves contained saponin, furanocoumarine and flavonoids like coumarins and quercetins, alkaloids and coumarins in the stem-bark while rutins was in the fruit among others [7, 10, 21, 22]. Studies also reported that the fruit-mesocarp contains protein, sugars, organic acids, other constituents like 3-rutinoside and 3-rhamnogalactoside of isorhamnetin [22], diosgenin [30], and a mixture of 22R and 22S epimers of 26-(Oβ-D-glucopyranosyl)-3-β-[4-O-(β-D-glucopyranosyl)-2-O-(α-L-rhamnopyranosyl)-β-D-luco pyranosy-loxy]-22,26dihydroxy furost-5-ene. The kernel contained

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xylopyranosyl derivative of the above saponin present in mesocarp [31] while nine saponins have been reported from the kernel cake [32]. The leaves and fruit kernels were found to contain six diosgenin glucosides including di-, tri-, and tetraglucosides [33]. The bark contains furanocoumarin bergapten and dihydrofuranocumarin D-marmesin [7,34]. It also contains beta-sitosterol, bergapten, marmesin, and beta-sitosterol glucoside [35,36,37,38, 39].

The hypoglycemic properties of *Balanites* aegyptiaca have been attributed to the presence of some of the above mention compounds. Kamel *et al*. [6] found two steroidal saponins from one of the active extract-fraction of the aqueous extract of *Balanites aegyptiaca* fruit after treating a diabetic mice by an oral administration. The study reported that the aqueous extract of the fruit mesocarp, as well as the polysaccharide fraction (precipitated by an excess of alcohol) and the supernatant (saponin-rich), exerted significant antidiabetic activities in STZ-induced diabetic mice.

A study conducted by Motaal *et al*. [10] has reported that different extracts and fractions of *Balanites aegyptiaca* fruit in cultured C2C12 skeletal muscle cells and 3T3-L1 adipocytes exerted antidiabetic activities. It was reported that 200 µg/ml of the sugars fraction (A1) showed the highest activity, it increased basal glucose uptake by 52 % in muscle cells; which is twice the activity of 100 nM insulin [insulin equivalent (IE) = 2.0 ± 0.07]. Whereas, dichloromethane (E) and ethyl acetate (F) successive extracts exerted 37 and 41 % increase in the glucose uptake, and accelerated triglyceride accumulation in pre-adipocytes undergoing differentiation, comparably with 10 µM rosiglitazone [rosiglitazone equivalent (RE) was 1.6 ± 0.3 and 0.7 ± 0.1) respectively. Gas chromatography (GC) analysis of the A1 revealed the presence of xylose, rhamnose, sorbitol, fructose, galactose and glucose while extracts E and F when standardized by high-performance liquid chromatography (HPLC) was reported to contained 0.031 and 0.239 % rutin and 0.007 and 0.004 % isorhamnetin, respectively.

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A study by Al-Malki *et al*. [20] reported that treating diabetic rats with ethyl acetate extract (EAE) of *Balanites aegyptiaca* fruit at 10, 25 and 50 mg /kg body weight resulted in a significant reduction in blood glucose levels. The GC-MS analysis of EAE of fruits of *Balanites aegyptiaca* revealed the presence of vanillic acid (26.58%) with the molecular formula $C_8H_8O_4$, and MW 312, syringic acid (24.08%) with molecular formula $C_9H_{10}O_5$, and MW 342 and, β-sitosterol (23.94%) with molecular formula $C_{29}H_{50}O$ and MW of 414. Shafik *et al*. [16] reported that, 50 mg/kg body weight of seed kernel of *Balanites aegyptiaca* exerted antihyperglycemic and antilipid peroxidative effects as well as increased activities of enzymatic and non-enzymatic antioxidants in allonxan-induced diabetic rats. Phytochemical investigation of the ethanolic extract of the plant seed kernel using column and preparative paper chromatography resulted in 9 compounds; isorhamnetin 3-rutinoside, 3-robinobioside, 3-0-glucoside, 3-0-galactoside, 3,7-diglucoside, quercetin-3-glucoside, 3-rutinoside, aglycones quercetin, and isorhamnetin respectively.

A study has suggested that isorhamnetin glycosides in plants may be responsible for the antidiabetic effect and also reversed endoplasmic reticulum stress markers and the expression of enzymes regulating lipid metabolism [40]. Rutin has 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 [41]. 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 [42].

Recent study has reported some compounds in the leaf extract of *Balanites aegyptiaca* [18]. The compounds identified in Balanites aegyptiaca(L.) leaves following investigation on alpha amylase inhibitory effect were phenol, 2,4-bis(1,1-dimethylethyl)-alpha-D-glucopyranoside, methyl, 1-hexene, 3,5,5-trimethyl, neophytadiene, 1-hexanol, 4-methyl-6-Octen1-ol, 3,7-dimethyl-, propanoate, 16-heptadecenal, 2-hexadecen-1-ol, 3,7,11,15-tetramethyl-, [R-[R*,R*-(E)]]- (T-Phytol), 1H-Indene, 1-hexadecyl-2,3-dihydro-, 1-tridecanol, carbonic acid, neopentylcyclo hexyl methyl ester and cyclopentane methanol, alpha-cyclohexyl-2-nitro.

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4.0 ANTIDIABETIC MODE OF ACTION 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 [43,44]. *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.

Oxygen radical scavenging activity: According to Al-Malki *et al* [20] and Shafik *et al* [16], *Balanites aegptiaca* extract exert antioxidant activity to combat diabetes mellitus. Al-Malki *et al* [20] studied the effect of ethyl acetate extract (EAE) of Balanites aegyptiaca fruit (10, 25 or 50 mg/kg body weight) in experimental diabetic rats. Rats were allocated into five groups; control, diabetic, and diabetic rats treated with 10, 25, and 50 µg/kg body weight of EAE for eight weeks. The results reported a protective role of EAE against oxidative stress induced by streptozotocin. It showed that EAE treatment produced a reduction in blood glucose levels, HbA1c, malondialdehyde and vascular endothelial growth factor (VEGF) in diabetic retina as well as enhanced antioxidant capacity against streptozotocin-induced oxidative stress. Al-Malki *et al*. [20] reported that *Balanites aegyptiaca* fruit extract has potential benefits in the prevention of retinopathy in diabetes via inhibition of free radical production and enhancement of antioxidant potential.

Shafik *et al*. [16] reported increased antioxidant status like SOD, catalase, GSHPs and decline in TBARS concentration in diabetic treated rats suggesting its potent antilipid peroxidative and antioxidative effects. About 500 g of Balanites aegyptiaca seeds kernel were dried, powdered

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and then soaked in 1500 ml of 95% ethanol overnight. After filtration, the residue obtained was again resuspended in equal volume of 95% ethanol for 48 hours and filtered again. The above two filtrates were mixed and the solvent was evaporated in a rotavapour at 40-50^{0}C under reduced pressure. Diabetic rats were orally administered 50mg/kg body weight of *Balanites aegyptiaca* seeds kernel extract. Results showed oral administration of *Balanites aegyptiaca* seed kernel at a dose of 50 mg/kg body weight significantly exerted antihyperglycemic and antilipid peroxidative effects as well as increased the activities of enzymatic antioxidants and levels of non enzymatic antioxidants

Increase insulin secretion: *Balanites aegyptiaca* extract was reported to have stimulated insulin secretion to lowered blood glucose levels [11, 14]. Samir *et al*. [11] have reported that oral administration of both aqueous and ethanolic extract of *Balanites aegyptiaca* significantly increased serum insulin levels in diabetic treated rats. Fruit flesh was used, it was extracted with water and ethanol separately using soxhlet apparatus for about 10 hours. About 80 mg/kg body weight of either the aqueous or ethanolic extracts were administered to the diabetic-induced rats groups for 30 days. The result showed that oral administration of aqueous or ethanolic extracts from Balanites aegyptiaca fruit flesh for 30 days to diabetic rats induced a highly significant decrease ($P< 0.01$) of serum glucose level, increased liver glycogen content, induced significant increase ($P< 0.05$) of serum insulin level but decreased glucagon level. It was suggested that the anti-diabetic effect of *Balanites aegyptiaca* fruit flesh was attributable in part to the increased in serum insulin concentration.

Alpha amylase inhibitory activity and insulinomimetic effect: In a study on antihyperglycemic effect of *Balanites aegyptiaca* in STZ-induced diabetic rats, it was reported that the antihyperglycemic effect of the *Balanites aegyptiaca* was mediated through insulin mimetic effect and inhibition of intestinal α-amylase activity [15]. It was also 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]. In a same study, the plant extract was reported to have inhibited α-amylase activity in a dose-dependent manner [15].

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Gad *et al* [15] studied the effects of 21 days oral administration of Balanites aegyptiaca fruit extracts (1.5g/kg body weight) on the liver and kidney glycogen content and glucose-6-phosphatase, glucose6-phosphate dehydrogenase and phospho-fructokinase in STZ-diabetic rats while α-amylase activity was studied in vitro. Mesocarps of the fruits were scraped off and extracted with boiling water (2 × 4l) for 4h. The extract was distilled and concentrated under reduced pressure and finally air spray-dried to give a light brown powder which was used for the study. The results showed reduced blood glucose level by 24% and significantly decreased liver glucose-6-phosphatase activity but glucose 6-phosphate dehydrogenase and phosphofructokinase were significantly increased in diabetic treated rats. On the other hand, in vitro inhibition of α-amylase activity was recorded.

Gawade and Farooqui [18] have also reported an *in vitro* inhibition of alpha amylase activity by Balanites aegyptiaca leaf extract. The study used *Balanites aegyptiaca*(L.) air dried leaves which were crushed into powdered and about 10 g was mixed in 100 ml of ethanol and kept on a magnetic stirrer for 2 hours and extracted using a soxhlet apparatus sequentially in ethanol. The activity was investigated through the inhibition of α-amylase. Acarbose at a concentration of (20100µg/ml) was used while ethanol extract at 20-100µg/ml was used. Result showed that acarbose showed α-amylase inhibitory activity from 47.17% to 68.81% with an IC50 value 27.90µg/ml, whereas ethanol extract (20-100µg/ml) of *Balanites aegyptiaca*(L.) showed potent inhibition activity in a dose dependent manner from 39.96% to 53.02% with an IC50 value of 84.08µg/ml.

Enhanced glucose uptake: 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 plants extract 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

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kinase (AMPK) pathway [45, 46]. The study used *Balanites aegyptiaca* fruits (1 kg) which was defatted with n-hexane and successively extracted by maceration in dichloromethane, ethyl acetate, methanol and water to obtain the extracts. The glucose uptake in muscle cells was studied with C2C12 cell line. Result showed extracts of *Balanites aegyptiaca* fruit exhibited similar significant activities on differentiated C2C12 myotubes as shown by their activities relative to an optimal dose of insulin (100 nM; insulin equivalents, IE: values of 0.7 ± 0.03, 0.6 ± 0.02, 0.7 ± 0.02 and 0.8 ± 0.02, respectively). *Balanites aegyptiaca* leaf extract in a recent study was reported to have stimulated erythrocytes glucose uptake in type II diabetic patients according to Mahdy *et al* [17].

Regeneration of beta cell of the pancreas: A study has reported that *Balanites aegyptiaca* extract was able to ameliorate beta-cell dysfunction [13].The study used fifteen adult male albino rats which were divided into two groups; group 1: control group, group 2: alloxan induced diabetic rats that were divided into two subgroups; subgroup1: diabetic untreated rats, subgroup 2: diabetic treated with aqueous extract of Balanites aegyptiaca (seeds). Results showed diabetic rats group treated with the plant seeds extract ameliorated most of the toxic effects of alloxan and showed partially improvement in histological changes produced by alloxan. It was concluded that, treating diabetic rats with water extract of Balanites aegyptiaca seeds ameliorated β-cells dysfunction and increased insulin's receptors sensitivity associated with improved in general diabetic conditions. Some of the *Balanites aegyptiaca* compounds with antidiabetic properties and likely mode of actions are 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 steroidal 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,

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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.

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

S No.	Plant Parts	Frequency of Part Used Based on Article published	Percent Frequency
1	Fruit	8	61.54
2	Seeds	3	23.07
3	Leaf	2	15.38

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

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, Isorhamnetin-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-rutinoside, 3-robinobioside, 3-0-glucoside, 3-0-galactoside, 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), neophytadiene, 3,7, 11,15-tetra methyl-[R-[R*, R*-(E)]-(T-phytol)	Inhibition of alpha amylase activity	[18]

-- = not specified

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