Anti-diabetic effects of *Holarrhena antidysentrica* extracts: Results from a Longitudinal Meta-analysis

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Abbreviations: CI, confidence interval; HA, Holarrhena antidysenterica; mRNA, messenger ribonucleic acid; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SMC, standardized mean change; SMD, standardized mean difference; STZ, Streptozotocin;

Abstract

Background:

Holarrhena antidysenterica (HA), a twining shrub belonging to the Apocynaceae family is found in tropical regions of Africa and over a large part of Asia including India, Philippines and Malayan Peninsula. In Indian traditional system of medicine, HA has been used to treat gastric ailments, for wound healing and also to improve glycaemic control. Glucose lowering activity of HA root, bark, seed, leaf and fruit extract in different parts of India as well as in Chinese traditional medicine is widely reported.

Purpose:

In the meta-analysis reported in this article, we summarize glucose-lowering effects of HA extracts from different plant parts as reported in multiple studies involving animal models of diabetes. Our analysis helps to quantify the glucose-lowering effect of HA in comparison with standard diabetes drugs. The analysis also sheds light on differential efficacy levels of HA extracted from different plant parts.

Study design:

The meta-analysis was carried out following PRISMA guidelines. Literature was searched to identify studies published between years 2011 to 2019 reporting glucose-lowering effects of HA extract on rodent models of diabetes.

Methods:

Longitudinal meta-analysis was carried out on time-course data extracted from selected studies to calculate standardized mean change of glucose value from day 1 to days 7, 14 and 21 post-treatment by HA extract or standard anti-diabetic drug. Subgroup analysis was carried out for studies reporting effects of HA on leaf and seed extracts. Standardized mean difference in levels of cholesterol, triglycerides and serum total protein between treatment and control groups were also assessed.

Results:

We shortlisted nine articles to be used for this meta-analysis. Summarized standardized mean changes of glucose value between day 1 and day 21 post-treatment indicated glucose-lowering effects of HA extracts to be marginally lower but comparable to that of standard anti-diabetic drugs like Glibenclamide or Sitagliptin. However, subgroup

61 analysis revealed seed extracts of HA to be more potent than leaf extracts or even
62 standard drugs. Effects of the extract on levels of cholesterol, triglyceride and serum total
63 protein was also commensurate with its glucose-lowering property.

64 *Conclusions:*

65 Our results, summarized over multiple studies, present a clear quantitative assessment
66 of the anti-diabetic property of HA, in particular the seed extracts compared to standard
67 anti-diabetic drugs. Further differential analysis of the seed extracts will be useful to
68 arrive at a herbal formulation with superior anti-diabetic property and possibly lesser
69 side effects than chemical entities.

Introduction

70

71 Diabetes mellitus is a chronic and serious metabolic disorder primarily manifested with
72 a hyperglycaemic condition as body is not able to produce sufficient quantity of Insulin
73 hormone or is not able to utilize the produced hormone. Latest Diabetic Atlas of
74 International Diabetic Foundation estimates around 463 million adults (20-79 years)
75 living with diabetes worldwide which is an astounding proportion of 9.3% of global adult
76 population(1). China, India and USA currently top the list of number of people with
77 diabetes and are likely to retain their unenviable ranking in the next ten years. Mortalities
78 in adults due to diabetes in 2019 was estimated as high as 4.2 million that is nearly twice
79 the 2.11 million deaths recorded due to COVID-19 till date(2).

80 Several classes of non-insulin pharmacological agents including sulfonylureas,
81 biguanides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase IV
82 inhibitors are currently used in clinic to improve glycaemic control. However,
83 undesirable side effects of many of these drugs often limit their use. On the other hand,
84 natural product-based anti-diabetics especially medicinal plants and herbal formulations
85 are very popular in many geographies due to their easy access, lesser cost and lesser side
86 effects. Several medicinal plants from middle-east Asia, China, south-east Asia including
87 India, Malaysia, Bangladesh, parts of Africa and Turkey have been documented in
88 literature for their use as anti-diabetics(3). In particular India has a large repertoire of
89 medicinal plants many of which have been used in traditional clinical practice to achieve
90 glycaemic control(4,5). Herbal formulations from these medicinal plants(6) and
91 phytocompounds derived from them (7) are shown to have glucose-lowering properties
92 which make them interesting alternatives for chronic use.

93 *Holarrhena antidysenterica* (HA), an Indian medicinal twining shrub, belonging to the
94 family Apocynaceae and commonly known as *Kurch* or *Kutaja* has been in use for long in
95 folklore therapy(8). HA is a major ingredient in several Ayurvedic preparations such as
96 *Bhunimbadi churna*, *Kutajghan Vati*, *Kutajarista* and *Kutaja churna*, that are used to treat
97 dysentery, diarrhoea, fever and bacterial infections traditionally in India. In modern
98 Ayurveda, HA is suggested for obesity, asthma, bronchopneumonia, hepatosplenomegaly,
99 rheumatism(9) diabetes, cancer and even for wound healing(10). It is also used as an
100 anti-oxidant and anti-depressant(11).

4

101   HA is studied extensively for treatment of metabolic diseases where the seed extract has
102   shown alpha-glucosidase activity in *in vitro* assay[12]. Ethanolic and methanolic extracts
103   of bark from HA shown inhibitory effect of glycemia[13]. Treatment of Streptozotocin
104   (STZ) induced diabetic rats or mice by extracts of HA from different plant parts including
105   seed, leaf and bark have resulted in lowering of blood glucose over a period of 7 to 21
106   days post-treatment[14–18]

107   Though many studies have indicated possible glucose-lowering and anti-diabetic activity
108   of HA extract, its usefulness in comparison with known anti-diabetic compounds is not
109   well established. Further, usage of various plant parts such as leaf and seed extracted with
110   different solvent adds heterogeneity and ambiguity in results. In this article, we attempt
111   to answer some of these questions by carrying out a careful meta-analysis of data
112   collected from literature on observed anti-diabetic effects of HA extracts in animal
113   models of diabetes in comparison with effects caused by standard anti-diabetic drugs like
114   Glibenclamide or Sitagliptin. With a number of studies reported in literature to assess the
115   anti-diabetic effects of HA extracts, to our knowledge this is the only meta-analysis study
116   aiming to compare summary effects of HA extract to the effect caused by standard drugs.

Meta-analysis Methods

Selection of Literature

119   We performed the meta-analysis following PRISMA guidelines[19]. Literature search was
120   performed in PubMed and Google Scholar for articles in English published between 2011
121   and 2019 with search terms *Holarrhena antidysenterica* in title or abstract. Studies with
122   STZ-induced diabetic rodent models were identified and included in meta-analysis.
123   Review articles, commentaries, opinions, individual case studies and articles with only *in*
124   *vitro* study results were excluded from analysis.

Data Extraction

126   Selected articles were reviewed independently by two authors (CAD and SKD). Values of
127   blood glucose and other parameters were extracted from articles using standardized
128   forms and was cross-validated. Standard errors of various parameters reported in all
129   selected studies except Keshri et al [20] were converted to standard deviation. Blood
130   glucose values reported in mmol/L unit [16] were converted to mg/dL using the
131   relationship 1 mmol/L = 18.018 mg/dL [21]. Dose values of extracts and reference drug

132   used, plant parts and solvents for extraction were recorded as mentioned in the articles.

133   One article (22) did not provide the data in tabular form, for which, data was extracted

134   from the graphs using WebPlotDigitizer online tool (23). For blood glucose time profile,

135   the start time was normalized to the day of administration of extract or reference drug.

136   ***Meta-Analysis and Meta-Regression***

137   Choice of appropriate statistics for longitudinal meta-analysis is crucial. To measure the

138   effect in change in blood glucose levels within the same group of animals we use a random

139   effects model on the standardized mean change (SMC) with raw score

140   standardization(24), between start of the treatment (day 1) and days 7, 14 and 21 post-

141   treatment separately for animals treated with HA extract or reference drug. For other

142   parameters, such as total cholesterol, triglycerides or serum protein measured at the end

143   of the study period, we use the standardized mean difference (SMD) of measured

144   parameter between treatment and diabetes control groups with Hedges' correction for

145   positive bias. All calculations were carried out using the Metafor library (25) on R

146   statistical software platform. Meta-regression of SMC of blood glucose between start and

147   day 21 of treatment was carried out using mixed-effects model with dose of the extract

148   (in mg/kg) and other categorical variables such as plant part and solvent used for

149   extraction as moderators.

150 # Results

151   ***Study Details***

152   The search yielded a total of 104 "hits" which were screened manually to select 9 articles

153   containing levels of blood glucose and other parameters measured in animal models of

154   diabetes (Fig. 1). All studies employed STZ-induced rodent models as the experimental

155   platform.

156   Different plant parts of *H. antidysenterica* such as leaf (18,22) and seed (15,16,20,26–29)

157   extracted with different solvents such as Ethanol, Ethyl acetate, Water, Petroleum ether

158   and Methanol were used for treatment of the animals. Leaf or seed were powdered after

159   air drying in shade and were extracted in a Soxhlet apparatus, employing respective

160   solvents. Concentrated extract was air dried at room temperature or under reduced

161   pressure and stored in air tight container in 2–8°C for use in experiments.

162 Some studies also compared glucose-lowering effects of standard drugs such as
163 Glibenclamide (16,18,20,26–28) or Sitagliptin (22) along with HA on same experimental
164 platform. Diabetes was induced by single intraperitoneal injection of STZ 50 mg/kg.
165 Development of diabetes was confirmed by fasting blood glucose estimation 72 h post-
166 STZ injection, wherein animals were fasted overnight before blood collection. Animals
167 with fasting blood glucose level above 200 mg/dL at 72 h after STZ injection were
168 considered diabetic and were included in experiments. Animals were randomly divided
169 into groups of 6 each and assigned for treatment. Plant extract was administered orally
170 every day in the dose range 100 – 600 mg/kg along with the reference drug at working
171 concentration from the day of induction of diabetes. Fasting blood glucose was measured
172 on days 1, 7, 14, 21 and 28 from start of the treatment.

173 Apart from serum glucose, most studies also reported values of other parameters
174 (Table 1) out of which only three parameters – serum cholesterol, triglyceride and total
175 protein were selected for meta-analysis since their values were reported in three or more
176 studies.

Longitudinal Meta-analysis of Blood Glucose Levels

178 From results of the studies, it is seen that administration of HA extract has glucose-
179 lowering effect over days 7 – 21 (Fig. 2). Results of longitudinal meta-analysis (Table 2)
180 reveal that the effect estimated as SMC (difference with day 1) increases progressively
181 from day 7 to day 21 for both HA extract as well as reference drug. On day 21, the effect
182 size of reference drug (12.93, 95% CI: 6.44, 19.42) is higher than the effect produced by
183 HA extract (9.53, 95% CI: 4.35, 14.70) (Fig. 3). However, results for HA extract showed
184 higher degree of heterogeneity (I^2 = 98.2%) compared to reference drug (87.3%)
185 indicating possible variations in the effect size of HA extract due to dose, plant part or
186 extraction solvent used.

Meta-Regression and Subgroup Analysis

188 Meta-regression of the serum glucose SMC on day 21 for HA extract with dose as
189 moderator did not show any statistically significant dependence of the SMC with dose of
190 extract administered (Supplementary Fig. 1). To estimate variations due to plant parts,
191 we performed the meta-analysis for the two subgroups, HA leaf and seed extracts used in
192 studies. This subgroup analysis results (Fig. 4) indicate that extract from seeds have
193 enhanced glucose-lowering ability (SMC 16.49, 95% CI: 7.99, 25.90) compared to that of

194 leaf (SMC 3.42, 95% CI: 0.55, 6.29). It explains major portion of the observed
195 heterogeneity of SMC of HA extract in Table 2. In all selected studies seeds were extracted
196 in ethanol, whereas ethanol, ethyl acetate and water were used for extraction of leaves.
197 Hence, we did not perform a separate subgroup analysis on the solvent as the results will
198 not be different than results of plant part subgroups. Nevertheless, it is important to note
199 that the seed extracts appear to be the most potent anti-diabetic fraction with a higher
200 glucose lowering effect than the observed effects of Glibenclamide or Sitagliptin.

201 *Meta-analysis of other Markers*

202 Meta-analysis of the other markers shows both HA extract and reference drugs reduce
203 total cholesterol (Supplementary Fig. 2) and triglycerides (Supplementary Fig. 3) in
204 serum on day 21 compared to the corresponding value in control diabetic animals who
205 did not receive any treatment. SMD value for reference drugs is higher than that of HA
206 extract (Table 3). However, for serum total protein, the reference drugs do not show any
207 statistically significant summary effect (p > 0.1) whereas with HA extract a marginally
208 significant effect (p = 0.051) is observed (Supplementary Fig. 4).

209 *Limitations*

210 Primary limitation of this meta-analysis is the nonuniformity of plant parts and extraction
211 solvent used across different studies. We performed subgroup analysis on the plant parts
212 to assess their differential effects on glucose-lowering. However, similar subgroup
213 analysis for extraction solvents could not be performed as ethanol was mostly used for
214 extraction of seeds. Most studies used Glibenclamide as the reference drug except one,
215 which compared the effect of Sitagliptin(22). However, for the comparison of anti-
216 diabetic effect with HA extract, we summarized effects of both drugs together. All selected
217 studies used the same number of animals (n = 6) for each treatment group, hence test for
218 publication bias due to differing number of samples was not carried out.

Discussions

220 Anti-diabetic properties of HA extract are well-known and is reported in many studies
221 including the ones synthesized in this meta-analysis. However, the consolidation of data
222 across multiple diverse studies clearly and quantitatively establishes the HA extract as a
223 potent anti-diabetic agent comparable to standard drugs like Glibenclamide and

224   Sitagliptin. Meta-analysis results for the effects of HA extract to lower the levels of serum

225   cholesterol and triglyceride and restore levels of serum total protein towards normalcy

226   further supports it's efficacy as an anti-diabetic.

227   An important finding from this meta-analysis is the dose independence of HA extract to

228   its observed glucose-lowering effect, that was not apparent from results of individual

229   studies. However, this is not an uncommon observation, as dose independence of

230   pharmacological effects of plant extracts were reported in studies with Musa AAA fruit

231   (30), leaf extracts of *K. Africana*(31) and *Camellia sinensis* green tea extract(32). Possible

232   explanation for this dose independent behaviour of HA extract could be the saturation of

233   active transport of phytochemicals to cells in 100 – 600 mg/kg dose range with the excess

234   amount getting excreted(33). Studies with HA extract at a lower dose range is

235   recommended to identify its dose-dependent anti-diabetic activity.

236   It's also important to note that seeds of HA extracted with ethanol showing markedly

237   higher glucose-lowering effect. A comparison of available data on phytochemicals

238   present in ethanol extract of seed and ethanol /ethyl acetate extracts of leaf (Table 4)

239   shows differential presence of triterpinoids like betulinic acid, oleanolic acid and amyrin

240   that are known anti-diabetic agents. STZ-induced diabetic mice treated with β-amyrin

241   showed reduction in the STZ-induced levels of blood glucose, cholesterol and

242   triglycerides(34). Similar glucose lowering effect on a STZ-nicotinamide induced diabetic

243   mice model was observed for treatment with betulinic acid(35). Oleanolic acid, another

244   triterpenoid, was also shown to reduce blood glucose in STZ-induced rats. This anti-

245   diabetic activity of oleanolic acid was associated with restoration of mRNA levels of anti-

246   oxidant enzymes glutathione peroxidase 1 and superoxide dismutase 1 in liver of

247   animals(36). It's likely that the anti-oxidant properties of these triterpenoid molecules

248   render their anti-diabetic potential. Quercetin, a flavonoid present in the seed extract is

249   also studied extensively for its anti-diabetic potential. A recent meta-analysis shows

250   glucose-lowering effect of quercetin in STZ or alloxan-treated diabetes model synthesized

251   over 13 different studies(37).

252   These results surely indicate the possibility of individual triterpinoids or flavonoids or

253   their combinations to render the enhanced anti-diabetic potential of HA seed extracts.

254   More detailed studies with differential identification of compounds between seed and

255 leaf extracts will perhaps unlock the true antidiabetic potential of HA as a herbal
256 formulation.

Conclusion

258 This meta-analysis conclusively summarizes the anti-diabetic effect of HA extract seen in
259 rodent diabetic models across 9 different studies. Ethanol extracts of HA seeds appear to
260 have more potent glucose-lowering ability than reference drugs like Glibenclamide and
261 Sitagliptin. Further, the HA extracts also lowered serum cholesterol and triglycerides and
262 restored total serum proteins in diabetic animals. Further studies on HA extracts can lead
263 to novel herbal formulations with anti-diabetic effects comparable to chemical
264 compounds.

Declaration of Interest

266 Authors declare that there are no conflicts of interest.

Author contribution

268 CAD: data curation and manuscript preparation, SKD: data curation, statistical analyses
269 and manuscript preparation, MD: conceived the project and manuscript review, MS:
270 manuscript review.

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Supplementary Material

279 Supplementary information file enclosed

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402

Tables

Table 1: Baseline characteristics of selected studies

Reference	Plant part	Solvent	Animal Model	No of Animals	HA dose (mg/kg)	Ref drug used	Ref drug dose (mg/kg)	Glucose measurement day	Other parameters measured
(18)	Leaf	Ethanol	STZ induced Wister albino rats	6	200,400	Glibenclamide	5	1,7,14,21	Body weight, GPT and GOT
(26)	Seed	Ethyl acetate	STZ induced Wister albino rats	6	Not mentioned	Glibenclamide	0.6	1,7,14,21,28	Triglyceride, HDL, Cholesterol, LDL, VLDL, Protein, Albumin, Insulin, body weight, Hepato-somatic index, Reno-somatic index, Globulin, Uric acid, Creatinine, Urea and Blood urea nitrogen.
(16)	Seed	50% ethanol	STZ induced diabetic Sprague-Dawley rats	6	100, 300	Glibenclamide	1	1,7,14,21	Triglyceride, OGTT, Cholesterol, Lipids
(28)	Seed	Water, petroleum ether, methanol	STZ-induced diabetic Male wistar albino rats	6	250	Glibenclamide	10	Not measured	Triglyceride, Cholesterol, Protein, body weight, Urea

Reference	Plant part	Solvent	Animal Model	No of Animals	HA dose (mg/kg)	Ref drug used	Ref drug dose (mg/kg)	Glucose measurement day	Other parameters measured
(29)	Seed	Water	STZ induced diabetic wistar strain male albino rats	6	400	Glibenclamide	0.6	1,7,14,21,28	Haemoglobin, Glycosylated Hb, Insulin, Body weight, creatinine, urea, GPT, GOT, ALP,
(22)	Leaf	Ethyl acetate	STZ-induced diabetic Wistar rats	6	100, 200, 400	Sitagliptin	3	1,7,14,21,28	Triglycerides, HDL, OGTT, Cholesterol, LDL, VLDL, Haemoglobin, Glycosylated Hb, Liver and Skeletal muscle glycogen, albumin, Insulin, Body weight, food and water intake,
(27)	Seed	90 % Ethanol	STZ-induced diabetic Male albino wister rat	6	300	Glibenclamide	5	1,7,14,21,28	Body weight
(15)	Seed	Water	STZ-induced diabetic wister male albino rats	6	600	Not mentioned		1,7,14	Triglycerides, HDL, LDL, VLDL, Liver and Skeletal muscle glycogen, body weight, hexokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, Liver and kidney GOT and GPT.

Reference	Plant part	Solvent	Animal Model	No of Animals	HA dose (mg/kg)	Ref drug used	Ref drug dose (mg/kg)	Glucose measurement day	Other parameters measured
(20)	Seed	90 % Ethanol	STZ-induced diabetic albino rats	6	300, 600	Glibenclamide	5	1,7,14,21,28	Triglycerides, OGTT, Protein, body weight, uric acid, creatinine, Urea, AST, ALP, ALK

STZ: Streptozotocin, GPT: Glutamic Pyruvic Transaminase, GOT: Glutamic Oxaloacetic Transaminase, HDL: High Density lipoprotein, LDL: Low Density lipoprotein, VLDL: Very Low-Density lipoprotein, OGTT: Oral Glucose Tolerance Test, ALP/ALK: Alkaline phosphatase, AST: aspartate transaminase and ALT: alanine transaminase.

Table 2: Results of longitudinal meta-analysis of serum glucose after treatment with HA extract or reference drug

Day after Treatment	Treatment with HA Extract		Treatment with reference drug	
	Effect size (SMCR) on serum glucose with day 1 (95% CI)	Heterogeneity (I^2)	Effect size (SMCR) on serum glucose with day 1 (95% CI)	Heterogeneity (I^2)
Day 7	4.04 (1.41, 6,68) $p < 0.01$	97.2%	6.65 (2.97, 10.34) $p < 0.001$	89.3%
Day 14	7.18 (3.02, 11,34) $p < 0.001$	98.0%	10.65 (4,95, 16.35) $p < 0.001$	89.4%
Day 21	9.53 (4.35, 14.70) $p < 0.001$	98.2%	12.93 (6.44, 19.42) $p < 0.0001$	87.3%

Table 3: Meta-analysis results for the change of cholesterol, triglycerides and serum total protein between treatment and control group of animals

Parameter	Treatment with HA Extract		Treatment with reference drug	
	Effect size (SMD) with control group (95% CI)	Heterogeneity (I^2)	Effect size (SMD) with control group (95% CI)	Heterogeneity (I^2)
Cholesterol	-5.32 (6.89, -3.77) $p < 0.0001$	73.9%	-9.05 (-14.08, -4.02) $p < 0.01$	79.0%
Triglycerides	-6.03 (-7,44, -4.61) $p < 0.0001$	62.4%	-9.03 (-13.34, -4.71) $p < 0.0001$	83.2%
Serum Protein	3.44 (-0.01, 6.88) $p = 0.051$	96.5%	4.79 (-1,33, 10.91) $p > 0.1$	95.5%

Table 4: Comparison of phytochemicals present in ethanol extract of HA seed and ethanol / ethyl acetate extract of leaf

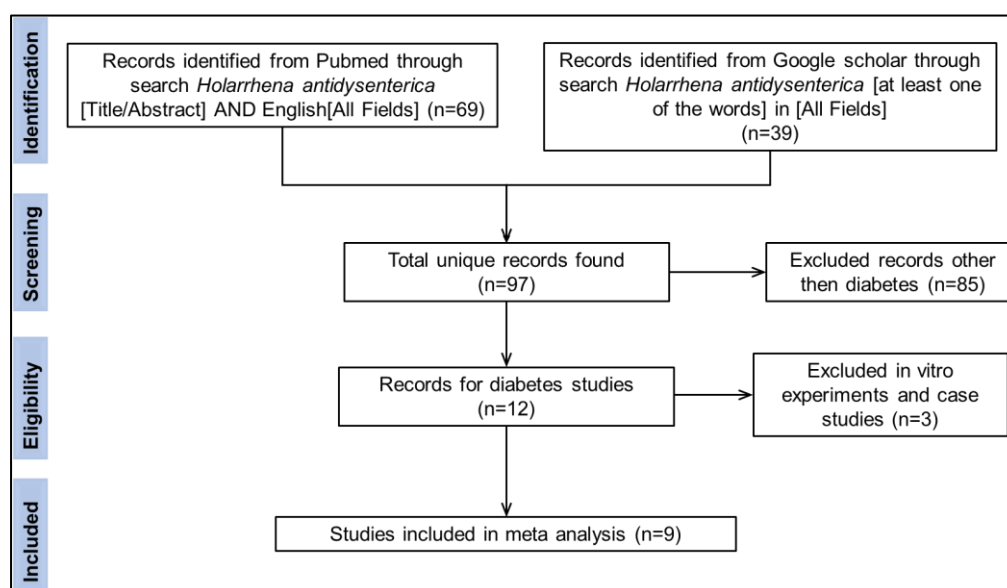| Plant part	Solvent	Compound	References
Seed	50 % Ethanol	alkaloids, carbohydrates, flavonoids including quercetin, tannins and phenolic compounds	(16)
Seed	90 % Ethanol	Alkaloids, carbohydrates, flavonoids, tannins and phenolic compounds, Saponins and steroids	(27)
Seed	Ethanol	Serine protease, pentacyclic triterpenoids, (lupeol, betulinaldehyde, and betulinic acid) steroidal compound (stigma sterol), dihydrocanaric acid, amyrin, betulin, and oleanolic acid	(38)
Leaf	Ethanol	Flavonoids, alkaloids, tannins and steroids	(18)
Leaf	Ethanol	Saponins, Amino acids, Phenol and Glycosides	(39)
Leaf	Ethanol	Terpenoids and reducing sugars	(40)
Leaf	Ethyl acetate	Total phenols, tannin and flavonoids	(22)
Leaf	Ethyl acetate	Flavonoids Alkaloids, Glycosides, Terpenoids, reducing sugars, Saponins, Tannins and Steroids	(40)

Figures

Figure 1: PRISMA flow diagram for literature search

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a

Author Year (dose)	Part	Solvent	Day 1	Day 21	Standardized Mean Change [95% CI]
Ali 2017 (400)	Seed	Water	331	109	24.58 [10.65, 38.51]
Bandawane 2019 (100)	Leaf	EtAc	534	271	1.45 [0.30, 2.60]
Bandawane 2019 (200)	Leaf	EtAc	261	193	1.16 [0.13, 2.20]
Bandawane 2019 (400)	Leaf	EtAc	447	181	1.60 [0.39, 2.81]
Hegde 2014 (200)	Leaf	Ethanol	323	142	8.22 [3.50, 12.94]
Hegde 2014 (400)	Leaf	Ethanol	330	124	8.33 [3.55, 13.11]
Keshri 2012 (300)	Seed	Ethanol	329	153	16.96 [7.33, 26.58]
Keshri 2012 (600)	Seed	Ethanol	328	140	18.16 [7.86, 28.47]
Kumar 2015 (300)	Seed	Ethanol	211	158	2.20 [0.72, 3.68]
Pathak 2015 (100)	Seed	Ethanol	240	142	15.56 [6.72, 24.40]
Pathak 2015 (300)	Seed	Ethanol	260	112	35.27 [15.30, 55.23]

RE Model (Q = 65.77, df = 10, p = 0.000; I^2 = 98.2%) 9.52 [4.35, 14.70]
p = 0.0003

Standardized Mean Change of Serum Glucose

b

Author Year	Day 1	Day 21	Standardized Mean Change [95% CI]
Ali 2017	337	103	18.68 [8.08, 29.28]
Ali 2018	297	89	13.99 [6.04, 21.95]
Bandawane 2019	341	213	1.29 [0.21, 2.38]
Hegde 2014	331	111	9.26 [3.96, 14.56]
Keshri 2012	333	120	29.82 [12.93, 46.71]
Kumar 2015	223	143	9.88 [4.23, 15.52]
Pathak 2015	262	107	22.62 [9.80, 35.45]

RE Model (Q = 54.05, df = 6, p = 0.000; I^2 = 87.3%) 12.93 [6.44, 19.42]
p = 0.0001
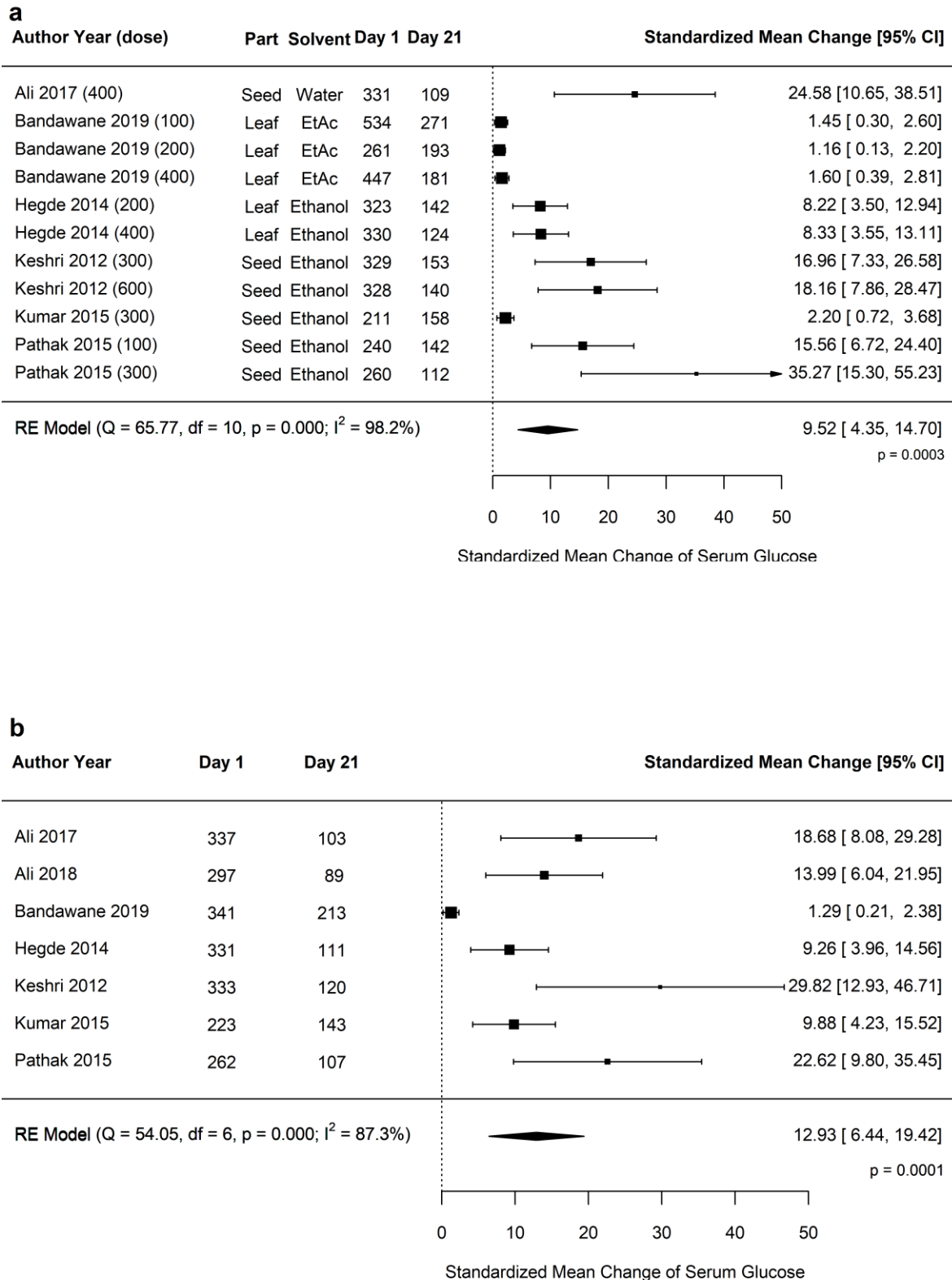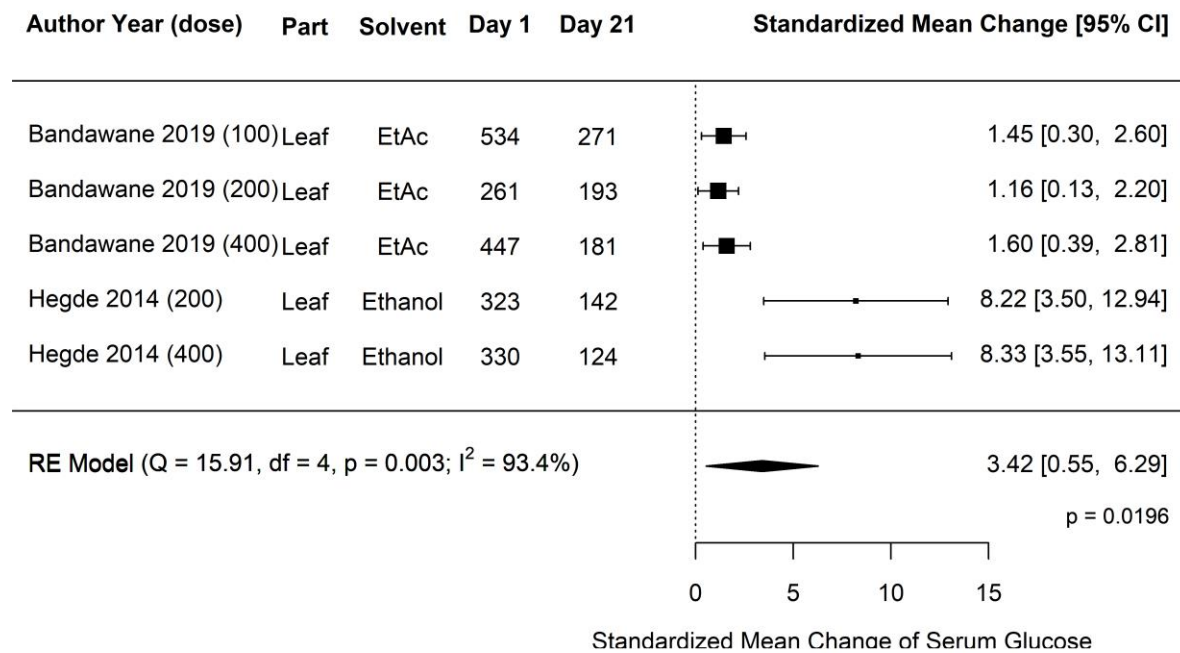
Standardized Mean Change of Serum Glucose

Figure 2: Effect on serum glucose by administration of HA extract

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Figure 3: Standardized mean change of serum in animals treated with (a) HA extract and (b) reference drug glucose between day 1 and day 21 post-treatment
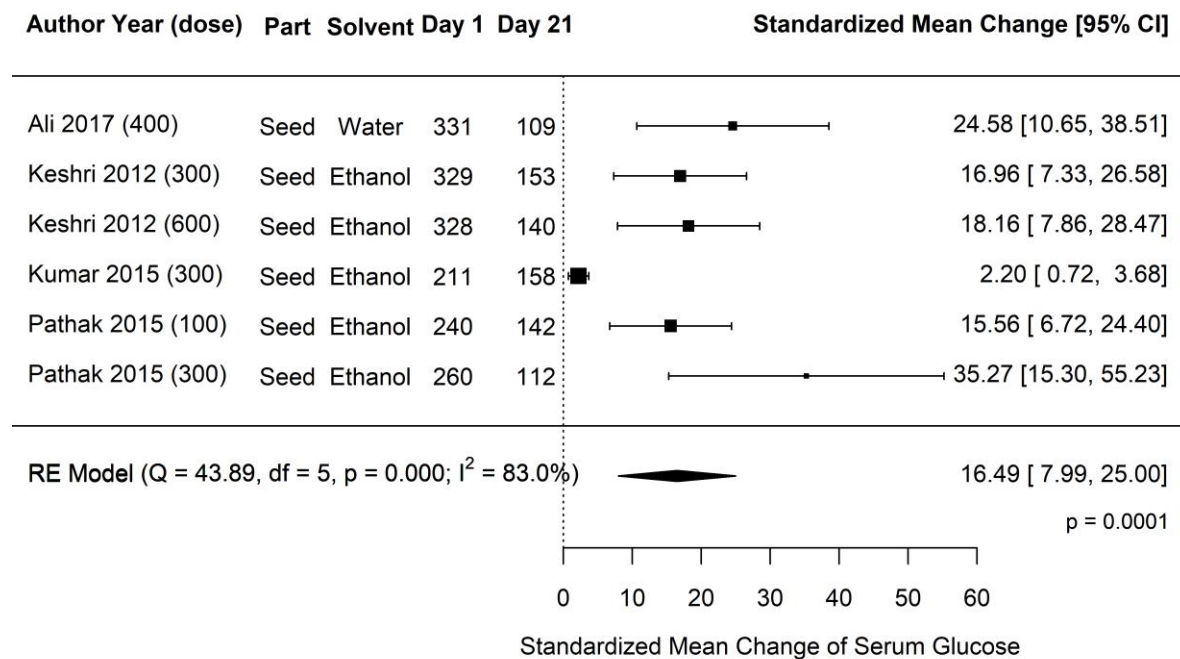
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Figure 4: Subgroup analysis of standardized mean change of serum glucose between day 1 and day 21 in animals treated with (a) HA leaf extract and (b) HA seed extract.

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