SOLANUM TORVUM FOR HYPERTENSION IN ‘KITAB AL-TIBB’: A SYSTEMATIC REVIEW ON THE SCIENTIFIC EVIDENCE

AZLINI ISMAIL
Department of Fundamental Dental and Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia.
dr_azlini@iium.edu.my
INTRODUCTION
Hypertension is a condition of high blood pressure.

1.13 billion of cases in 2015 throughout the world.

Local prevalence;
- 2000 -2010: 28.7%
- 2010 -2017: 29.2%

Uncontrolled blood pressure leads to CVS-associated mortality.

(Anuar & Ismail, 2020)
Available antihypertensive medications;
- undesirable side effects.
- high cost.

Alternative herbal ethno-medicinal plants (Ayurvedic & Traditional Chinese medicines).

Malay ethno-medicinal plants is yet under-explored.
Malays - have records utilizing local resources in dealing with various diseases/conditions.

Kitab Al-tibb:

✓ A Malay medical manuscript by Haji Ismail bin Haji Mustafa Pontianak.

✓ Malay medical experiences - 100 herbs/plants for 15 diseases.

2 plants for treatment of hypertension,

 ✓ terung pipit

 ✓ setawar

No further statement on which ‘setawar’ species, thus only Solanum torvum was included in this review.

Kitab Al-tibb:

✓ Kitab Al-tibb: Malay medical manuscript by Haji Ismail bin Haji Mustafa Pontianak.

✓ Malay medical experiences - 100 herbs/plants for 15 diseases.
SOLANUM TORVUM

- Local names:
  - Terung pipit in Malay (Abdul Hamid & Fauzi, 2012)
  - Turkey berry (Mohan et al., 2009)
  - Eggplant (Nwanna et al., 2014)
  - Sundaikai or kodusonde in India (Rammohan et al., 2011)
  - Ma khaeong in Thailand (Inta et al., 2013)
  - Bang Guo in China (Yang et al., 2020)

- Family: Solanaceae
- An erect shrub and widely-branched (Mohan et al., 2009).
- Found in Africa, West Indies (Mohan et al., 2009), Asia, and South America (Li et al., 2014).
- Fruits are edible, used as vegetables among Malay, Thai, Indian, and Chinese.
**PROBLEM STATEMENT**

No systematic study has been done to establish body of evidences for the use of S. torvum for hypertension as stated in ‘Kitab al-Tibb’ or ‘Kitab Tibb Pontianak’.

**HYPOTHESIS**

The use of S. torvum for hypertension as stated in ‘Kitab al-Tibb’ or ‘Kitab Tibb Pontianak’ is supported by the modern scientific evidences.

**OBJECTIVE**

To conduct systematic review asserting the use of S. torvum for hypertension as stated in ‘Kitab al-Tibb’ or ‘Kitab Tibb Pontianak’ in the modern scientific evidence.
METHODOLOGY
SEARCH STRATEGY

"Solanum torvum" OR "S. torvum" AND ("antihypertensive" OR "anti-hypertensive" OR "diuretic" OR "vasodilation" OR "ACE inhibitor" OR "angiotensin converting enzyme inhibitor" OR "blood pressure").

• No date and language restrictions.

International Conference on Malay Medical Manuscripts 2020, 15-16th December 2020
INCLUSION CRITERIA

All articles on S. torvum with either:

- **In vivo study** (effect on blood pressure or diuretic effect)
- **In vitro studies** on isolated blood vessels
- **In vitro studies** regarding inhibition of angiotensin-converting enzymes (ACE) - related to antihypertensive mechanism
- Field surveys on the use for hypertension
- Chemical analysis

EXCLUSION CRITERIA

Articles that were **not** original research articles i.e.:

i. review articles
ii. book chapters
iii. conference abstracts and papers
iv. short communications
v. other types of sources
FINDINGS
122 records;
- 110 results (Science Direct)
- 11 results (SCOPUS)
- 1 result (PUBMED)

3 duplicates identified and removed

119 records screened

63 records screened (title & abstract) for relevance with the scope of this review

Records included in this review, n=17

FLOW CHART FOR SYSTEMATIC REVIEW

56 records excluded - not original research articles

46 records excluded - did not fulfil inclusion criteria

International Conference on Malay Medical Manuscripts 2020, 15-16th December 2020
## RECORDS AND TYPES OF STUDY

<table>
<thead>
<tr>
<th>RECORD NO.</th>
<th>TYPE OF STUDY</th>
<th>REFERENCES</th>
</tr>
</thead>
</table>
| 1          | • In vitro ACE inhibition study.  
            • Traditional use for hypertension. | Simaratanamongkol et al. (2014a) |
| 2          | • In vitro ACE inhibition study. | Simaratanamongkol et al. (2014b) |
| 3          | • In vitro ACE inhibition study. | Nwanna et al. (2014) |
| 4          | • Traditional use for hypertension.  
            • In vivo study on rats (high-fructose diet).  
            • In vivo vascular reactivity test with catechomines. | Mohan et al. (2009) |
| 5          | • In vivo study on anesthetized normotensive rats (intravenous route).  
            • Study on the mechanism of action. | Nguelefack et al. (2008) |
| 6          | • In vivo study on rats on normotensive and L-NAME treated rats.  
            • In vitro study on isolated aorta rings.  
            • Study on the mechanism of contractile effect.  
            • Diuretic study. | Nguelefack et al. (2009) |
| 7          | • Diuretic study. | Rammohan et al. (2011) |

*ACE: angiotensin converting enzyme
# Records and Types of Study

<table>
<thead>
<tr>
<th>RECORD NO.</th>
<th>TYPE OF STUDY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Traditional use of <em>S. torvum</em> for hypertension. Chemical analysis study on aerial parts.</td>
<td>Lu <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>9</td>
<td>Chemical analysis study on fruits.</td>
<td>Pérez Colmenares <em>et al.</em> (2013)</td>
</tr>
<tr>
<td>10</td>
<td>Chemical analysis study on aerial parts. (steroidal glycosides).</td>
<td>Lu <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>11</td>
<td>Chemical analysis study on fruits (steroidal glycosides).</td>
<td>Li <em>et al.</em> (2014)</td>
</tr>
<tr>
<td>12</td>
<td>Chemical analysis study (polyphenols, carotenoids, and ascorbic acid content).</td>
<td>Andarwulan <em>et al.</em> (2012)</td>
</tr>
<tr>
<td>13</td>
<td>Chemical analysis study (non-alkaloidal constituents).</td>
<td>Mahmood <em>et al.</em> (1983)</td>
</tr>
<tr>
<td>14</td>
<td>Traditional use of dried fruits of <em>S. torvum</em> for hypertension.</td>
<td>Esakkimuthu <em>et al.</em> (2016)</td>
</tr>
<tr>
<td>15</td>
<td>Traditional use of <em>S. torvum</em> decoction for hypertension.</td>
<td>Inta <em>et al.</em> (2013)</td>
</tr>
<tr>
<td>16</td>
<td>Traditional use of <em>S. torvum</em> as plant with diuretic effect.</td>
<td>Sivapriya &amp; Leela (2007)</td>
</tr>
<tr>
<td>17</td>
<td>Traditional use of <em>S. torvum</em> fruits for hypertension.</td>
<td>Ong &amp; Nordiana (1999)</td>
</tr>
</tbody>
</table>
FREQUENTLY-USED PARTS OF S. TORVUM

- Fruits: 70%
- Aerial parts: 12%
- Not indicated: 12%
- Leaves: 6%

COUNTRY OF ORIGIN

<table>
<thead>
<tr>
<th>Country</th>
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<td>Venezuela</td>
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<td>Thailand</td>
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</tr>
<tr>
<td>Malaysia</td>
<td>1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1</td>
</tr>
</tbody>
</table>

International Conference on Malay Medical Manuscripts 2020, 15-16th December 2020
Record #10: Lu et al. (2009)

- Four steroidal glycosides isolated from S. torvum fruits in China:
  1. solanolide 6-O-[L-rhamnopyranosyl(1 → 3)]O-D-quinovopyranoside
  2. solanolide 6-O-[D-xylpyranosyl(1 → 3)]O-D-quinovopyranoside
  3. Yamogenin 3-O-[D-glucopyranosyl(1 → 6)]O-D-glucopyranoside
  4. neochlorogenin 3-O-[D-glucopyranosyl(1 → 6)]O-D-glucopyranoside

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Record #9: Pérez Colmenares et al. (2013)

- Seven steroidal glycosides isolated from S. torvum fruits in Venezuela:
  1. (25S)-26-(β-D-glucopyranosyloxy)-3-oxo-5α-furost-20(22)-en-6α-yl-O-b-D-xylpyranoside
  2. (25S)-26-(β-D-glucopyranosyloxy)-3-oxo-22α-methoxy-5α-furostan-6α-yl-O-b-D-xylpyranoside
  3. (25S)-3β-glucolpyranosyloxy)-3β-hydroxy-22α-methoxy-5α-furostan-6α-yl-O-a-L-rhamnopyranosyl(1 → 3)]O-b-D-glucopyranoside
  4. (25S)-3β-hydroxy-5α-spirostan-6α-yl-O-b-D-xylpyranoside
  5. (25S)-3β-oxo-5α-spirostan-6α-yl-O-b-D-xylpyranoside
  6. (25S)-3β-hydroxy-5α-spirostan-6α-yl-O-b-D-glucopyranoside
  7. (25S)-3β,27-dihydroxy-5α-spirostan-6α-yl-O-b-D-glucopyranoside.

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Record #11: Li et al. (2014)

- Five steroidal glycosides cytotoxic compounds isolated from S. torvum fruits in China:
  1. 25(S)-26-O-β-D-glucopyranosyl-5α-furost-22(20)-en-3β,6α,26-triol-6-O-[α-L-rhamnopyranosyl(1 → 3)]O-β-D-quinovopyranoside
  2. 25(S)-26-O-β-D-glucopyranosyl-5α-furost-22(20)-en-3-one-6α,26-diol-6-O-[α-L-rhamnopyranosyl(1 → 3)]O-β-D-quinovopyranoside
  3. 25(S)-26-O-β-D-glucopyranosyl-5α-furost-22(20)-en-3β,6α,26-triol-6-O-[β-D-quinovopyranoside]
  4. 5α-pregn-16-en-20-one-3β,6α-diol-6-O-[α-Lrhamnopyranosyl(1 → 3)]β-D-quinovopyranoside
  5. 5α-pregn-16-en-3,20-dione-6α-ol-6-O-[α-L-rhamnopyranosyl(1 → 3)]β-D-quinovopyranoside
CHEMICAL COMPOUNDS IN S. TORVUM

Record #13: Mahmood et al. (1983)

- Nine non-alkaloidal compounds isolated from S. torvum leaves in India:
  1. 2,3,4-trimethyltriacontane
  2. octacosanyl triacontanoate
  3. S-hexatriacontanone
  4. Triacontanol
  5. 3-triatriacontanone
  6. tetraatriacontanoic acid
  7. sitosterol
  8. Stigmasterol
  9. campesterol

Record #12: Andarwulan et al. (2012)

- Do not involve isolation of compounds, but determination of polyphenols, carotenoids, ascorbic acid content of S. torvum fruits in Indonesia.

Record #8: Lu et al. (2011)

- Nine compounds isolated from S. torvum aerial parts in China:
  1. neochlorogenic 6-O-β-D-quinovopyranoside
  2. neochlorogenic 6-O-β-D-xylopyranosyl-(1→3)-β-D-quinovopyranoside
  3. neochlorogenic 6-O-α-Lrhamnopyranosyl-(1→3)-β-D-quinovopyranoside
  4. solagenin 6-O-β-D-quinovopyranoside
  5. solagenin 6-O-α-Lrhamnopyranosyl-(1→3)-β-D-quinovopyranoside
  6. isoquercetin
  7. rutin
  8. kaempferol
  9. quercetin

Antihypertensive effects of flavonoids via various underlying mechanisms (Maaliki et al., 2019).
Aqueous and methanolic extract of *S. torvum* fruits (i.v.) induced a significant reduction in arterial blood pressure of normotensive rats, comparable to verapamil (Nguelefack et al., 2008).
IN VIVO STUDY (ORAL ROUTE, NORMOTENSIVE AND L-NAME INDUCED HYPERTENSIVE RATS)

(Nguelefack et al., 2009)

• Aqueous extract of S. torvum fruits amplified the hypertensive effect of rats given N (gamma)-nitro-L-arginine methyl ester (L-NNAME, nitric oxide synthase inhibitor).
• The same effect was not observed in normotensive rats.
Aqueous extract of *S. torvum* fruits induced a marked diuretic effect in L-NAME (nitric synthase inhibitor)-treated rats.
Aqueous extract of *S. torvum* fruits have potent dose-dependent *in vitro* vasocontractile activity.

(Nguelefack et al., 2009)
**IN VIVO STUDY (ORAL ROUTE, FRUCTOSE INDUCED HYPERTENSIVE RATS)**

High fructose diet (fructose 10%, w/v) for induction of hypertension

6-week intervention with *S. torvum* (p.o daily)

- Orally-fed ethanolic extract significantly decreased blood pressure elevation induced by high-fructose diet.

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**Effect of *Solanum torvum* on blood pressure and metabolic alterations in fructose hypertensive rats**

Mahaalaxmi Mohan a, b, Bhagat Singh Jaiswal a, b, Sanjay Kasture b

* a Department of Pharmacology, RECCL's Pharmacy College, Pune, Maharashtra, India
  b School of Life Sciences, University of Pune, Maharashtra, India

Fig. 1. Effect of *Solanum torvum* (100 mg/kg and 300 mg/kg, p.o., for 6 weeks) on SBP (mmHg) in fructose (10%) induced hypertensive rats. N=5, all values are expressed as mean ± SEM. All data are subjected to one-way ANOVA followed by Dunnett’s test. *p < 0.05 when compared to control and #p <0.05 when compared to fructose-fed group. F = fructose (10%), ST = *Solanum torvum*. Nif = Nifedipine.
IN VIVO STUDY (ORAL ROUTE, FRUCTOSE INDUCED HYPERTENSIVE RATS)
(Mohan et al., 2009)

High fructose diet (fructose 10%, w/v) for induction of hypertension

6-week intervention with *S. torvum* (p.o daily)

Anaesthetized with urethane

100 & 300 mg/kg (p.o) macerated ethanolic extract reduced the basal blood pressure in fructose-fed rats - comparable to standard drug, nifedipine (10 mg/kg/day, p.o.).
Ethanol extract of S. torvum fruits significantly reduced vascular reactivity to catecholamines - comparable to standard drug, nifedipine (10 mg/kg/day, p.o.).
Fruit wall methanolic extracts of *S. torvum* showed effective diuretic activity (increasing total urine output and increased sodium excretion).

**DIURETIC ACTIVITY**
(Rammohan et al., 2011)

Fruit wall and seed methanolic extracts of *S. torvum* (p.o) fed on normotensive Wistar rats

**Table 1: Diuretic activity of seed and fruit wall extracts of *Solanum torvum***

<table>
<thead>
<tr>
<th>Name of the drug/extracts</th>
<th>Dose (mg/kg)</th>
<th>Volume of urine in ml (Mean ± SEM) After 5 hrs</th>
<th>Electrolyte excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Na⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cl⁻</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>0.6±0.04</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>Standard (furosemide)</td>
<td>20</td>
<td>3.2±0.44</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>112</td>
</tr>
<tr>
<td>Seed methanol</td>
<td>150</td>
<td>0.9±0.13</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>1.2±0.06</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>450</td>
<td>1.4±0.13</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>13.1</td>
</tr>
<tr>
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<td>81</td>
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<tr>
<td>FruitWall methanol</td>
<td>150</td>
<td>1.7±0.04</td>
<td>98</td>
</tr>
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<td>12.5</td>
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<td></td>
<td></td>
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<td>87</td>
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<tr>
<td></td>
<td>300</td>
<td>2.0±0.02</td>
<td>114</td>
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<td></td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>450</td>
<td>2.3±0.13</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>101</td>
</tr>
</tbody>
</table>
IN VITRO ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORY STUDY

(Nwanna et al., 2014; Simaratanamongkol et al., 2014a,b)
IN VITRO ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORY STUDY

(Nwanna et al., 2014)

- Aqueous extract of S. torvum fruits collected from Nigeria exhibited significant ACE inhibitory activity with IC\textsubscript{50} of 106 ± 0.01 µg/ml.
IN VITRO ANGIOTENSIN CONVERTING ENZYME INHIBITORY STUDY

(Simaratanamongkol et al., 2014a)

- Methanol extract (5mg/ml) of *S. torvum* fruits from Thailand exhibited significant ACE inhibition activity of 76.2%.

Identification of a new angiotensin-converting enzyme (ACE) inhibitor from Thai edible plants

Arunee Simaratanamongkol¹, Kaoru Umehara¹, Hiroshi Noguchi¹, Pharkphoom Panichayupakaranant²,³,⁴

¹Department of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand
²Pharmaceutical Analytical and Pharmaceutical Biotechnology Excellence Center, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand
³School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan

3. Results and discussion

Prior to determination of the ACE inhibitory activity of these plant extracts, the responsiveness of the assay system was calibrated with captorpril, a positive control, and it showed ACE inhibitory activity with an IC₅₀ value of 1.56 nM, which was in good agreement with a previous report (Nunes-Mamede, De Mello, & Martins, 1990). Among the sixteen extracts from eight Thai edible plants that were investigated for their ACE inhibitory activity, the methanol extract of *A. graveolens* gave the highest percentage of ACE inhibitory activity (82.3%, at a concentration of 5 mg/ml), and exhibited a significant IC₅₀ value of 1.7 mg/ml, followed by the methanol extract of *S. torvum* (76.2%, at a concentration of 5 mg/ml) and the ethyl acetate extract of *A. occidentale* (64.2%, at a concentration of 5 mg/ml). The other plant extracts showed only a weak inhibitory activity with a percentage of ACE inhibitory activity lower than 60% each tested at a concentration of 5 mg/ml (data not shown). Thus, these three edible plants may be able to contribute to hypotensive effects by being inhibitors of angiotensin converting enzyme in the renin-angiotensin system. The methanol extract of *A. graveolens* was the one selected and subjected to isolation of the ACE inhibitor.
### IN VITRO ANGIOTENSIN CONVERTING ENZYME INHIBITORY STUDY

(Simaratanamongkol et al., 2014b)

<table>
<thead>
<tr>
<th>Extract/Compound/Drug</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol extract</td>
<td>1.2 mg/ml</td>
</tr>
<tr>
<td>(E)-2,3-dihydroxycyclopentyl-3-(3′,4′-dihydroxyphenyl)acrylate</td>
<td>778 µg/mL</td>
</tr>
<tr>
<td>Captopril</td>
<td>3.25 nM</td>
</tr>
</tbody>
</table>

**Figure 1** - Isolation of secondary metabolites from S. torum.

(E)-2,3-dihydroxycyclopentyl-3-(3′,4′-dihydroxyphenyl)acrylate
SUMMARY &
CONCLUSION
Plausible evidences;

✓ Reduction in basal blood pressure and the blood pressure elevation induced by high fructose diet (Mohan et al., 2009).

✓ Reduced vascular reactivity to catecholamines in high fructose-induced hypertension (Mohan et al., 2009).

✓ Diuretic activity by increasing total urine output and increased sodium excretion in normotensive rats (Nguelefack et al., 2009; Rammohan et al., 2011).

✓ Significant inhibition on angiotensin-converting enzyme (Nwanna et al., 2014; Simaratanamongkol et al., 2014a, 2014b)

Implausible evidences;

i) Enhanced blood pressure elevation in L-NAME-treated rats (Nguelefack et al., 2009)

ii) Contractile effect on the isolated aorta rings of normal rats. (Nguelefack et al., 2009)

• These discrepancies actually suggest that *S. torvum* works distinctively in different animal models of induced-hypertension.
**SUGGESTION**

- Thus, there is a need to **conduct further study on Spontaneously Hypertensive Rats model** that mimics the essential hypertension that frequently occurs in human.

**CONCLUSION**

- This review found **scientific evidences from modern science supporting the use of S. torvum as mentioned in ‘Kitab al-Tibb’ for hypertension.**
REFERENCES


