Bitter gourd and anti-diabetics: biochemistry and mechanism
- A literature review -

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Bitter Gourd and Diabetes mellitus

- Bitter gourd (*Momordica charantia*): important market vegetable and medicinal plant mainly for blood glucose control

- Bitter gourd is the most often used complementary alternative medicine used by diabetic patients in Malaysia (Ching et al. 2013)

- Google: 170,000 results for “bitter gourd + diabetes”

- There are several juices, capsules, and teas commercially available

- Most products are sold without any scientifically proven information about safety, dosage, or effectiveness
Scientific Information on Bitter Gourd

Pubmed: around **170 results** for “bitter gourd + diabetes” published between 1963 and today

- Scientific data is also available on the treatment of **cancer, hypertension, and dyslipidemia**
- The scientific focus is on the **anti-diabetic** effects of bitter gourd
- Bitter gourd is high in nutrients and **bioactive compounds**
<table>
<thead>
<tr>
<th>Bitter gourd compound</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momordicoside S</td>
<td>Increased glucose clearance during intraperitoneal glucose tolerance test; increased basal metabolic rate and β-oxidation</td>
<td>[10]</td>
</tr>
<tr>
<td>Momordicoside T</td>
<td>Increased glucose clearance during intraperitoneal glucose tolerance test</td>
<td>[10]</td>
</tr>
<tr>
<td>5β,15–epoxy-3β,25–dihydroxycurcubita-6,23(E)-dien</td>
<td>Lowered blood glucose levels</td>
<td>[11]</td>
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<tr>
<td>Conjugated linolenic acid, linoleic acid, conjugated linoleic acid</td>
<td>Intestinal GLP-1 release</td>
<td>[12]</td>
</tr>
<tr>
<td>19-nor-cucurbita-5(10),6,8,22-(E),24-pentaen-3β-ol</td>
<td>Intestinal GLP-1 release</td>
<td>[12]</td>
</tr>
<tr>
<td>6,5β,19-epoxycucurbita-6,24-diene-3β,23ξ-diol (karavilagenine E)</td>
<td>Intestinal GLP-1 release</td>
<td>[12]</td>
</tr>
<tr>
<td>Oleanolic acid</td>
<td>Intestinal GLP-1 release</td>
<td>[12]</td>
</tr>
<tr>
<td>Trehalose</td>
<td>Lowered postprandial blood glucose levels</td>
<td>[13]</td>
</tr>
<tr>
<td>Momordin</td>
<td>PPAR β/δ activation</td>
<td>[14]</td>
</tr>
<tr>
<td>9c, 11t, 13t conjugated linolenic acid</td>
<td>PPARα and γ activation</td>
<td>[15]</td>
</tr>
</tbody>
</table>
Suggested Actions of Bitter Gourd on Blood Glucose

**CELL CULTURE AND ANIMAL STUDIES WITH BITTER GOULD (MOMORDICA CHARANTIA)**

- Inhibition of α-glucosidases
- Na⁺/K⁺ dependent glucose uptake↓
- GLP-1 secretion β-cell protection / recovery
- Overweight↓
- PPARγ activation
- Insulin signal transduction
- Inhibition of PTP 1B
- Insulin-like peptide
- AMPK activation
- Inhibition of α-glucosidases
- Na⁺/K⁺ dependent glucose uptake↓
- Intestinal glucose uptake↓
- Insulin secretion↑
- Glucose uptake of peripheral tissues↑

**Blood glucose levels ↓**

GLP-1 = glucagon-like peptide-1; PPARγ = peroxisome proliferator-activated receptor; PTP 1B = protein tyrosine phosphatase 1B; AMPK = AMP-activated protein kinase

Modified after Habicht et al. 2013
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- Sodium/potassium dependent glucose uptake ↓
- Intestinal glucose uptake ↓
- Glucose uptake of peripheral tissues ↑
- Blood glucose levels ↓

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Intestinal Glucose Uptake (2/2)

Uebanso et al. (2007):

• Healthy eight weeks old Sprague-Dawley rats (fasted)
• Bitter gourd extracts: water fraction, methanol soluble extract and methanol insoluble extracts from the water fraction
• 0.6 g/kg body weight orally / Control received water instead
• 1 g sucrose or glucose per kg body weight

⇒ No bitter gourd effect without administration of sucrose
⇒ All three bitter gourd treatments reduced blood glucose levels compared to the control after administration of sucrose ($p<0.05$)

However, in other studies with diabetic subjects, bitter gourd improved glucose tolerance
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**Intestinal glucose uptake ↓**

**Insulin secretion ↑**

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Insulin Secretion (1/3)

Sekar et al. (2005):

- Animal model: stz diabetic rats
- Water extracts of bitter gourd seeds
- 30 days of treatment with 150 mg/kg body weight

⇒ Bitter gourd prevented weight loss ($p<0.05$)
⇒ Improved blood glucose and HbA$_{1C}$ ($p<0.05$)
⇒ Improved glucose tolerance (oGTT) ($p<0.05$)
⇒ Lower activity of gluconeogenetic and glycogenolytic enzymes in the liver ($p<0.05$)
⇒ Higher glycogen concentration in the liver ($p<0.05$)
Insulin Secretion (2/3)

Ahmed et al. (1998):
• Male stz diabetic rats were treated daily with 10 mL per kg body weight of bitter gourd juice for nine weeks
  ⇒ It could be shown that the number of insulin positive cells was increased by this treatment ($p<0.005$)
  ⇒ The authors assume that bitter gourd juice protects and recovers pancreatic $\beta$-cells and, thus, increases insulin secretion

![Images of pancreas sections](https://via.placeholder.com/150)

non-diabetic control  diabetic control  diabetic + bitter gourd
**Insulin Secretion (3/3)**

**Huang et al. (2013):**

- Different extracts increased GLP-1 secretion from STC-1 enteroendocrine cells
- Extracts were tested in high fat diet treated mice in a single dosage

⇒ Fraction of small molecules lowered blood glucose and increased insulin and GLP-1
⇒ Exendin-9, a GLP-1 antagonist, reduced this effect
⇒ improved glucose tolerance after intraperitoneal GTT

<table>
<thead>
<tr>
<th>Group</th>
<th>Vehicle</th>
<th>WES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>395.7 ± 24.1</td>
<td>377.6 ± 40.9</td>
</tr>
<tr>
<td>30 min</td>
<td>411.5 ± 22.4</td>
<td>282.6 ± 24.2***</td>
</tr>
<tr>
<td>30 min−0 min</td>
<td>015.8 ± 24.1</td>
<td>−95.0 ± 39.3***,zz</td>
</tr>
<tr>
<td>Plasma insulin (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>0.78 ± 0.29</td>
<td>0.66 ± 0.34</td>
</tr>
<tr>
<td>30 min</td>
<td>0.46 ± 0.09</td>
<td>0.80 ± 0.35**</td>
</tr>
<tr>
<td>30 min−0 min</td>
<td>−0.32 ± 0.32*</td>
<td>0.15 ± 0.26*</td>
</tr>
<tr>
<td>Plasma GLP-1 (pM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>4.69 ± 1.96</td>
<td>4.60 ± 1.46</td>
</tr>
<tr>
<td>30 min</td>
<td>4.71 ± 1.86</td>
<td>8.18 ± 2.50***</td>
</tr>
<tr>
<td>30 min−0 min</td>
<td>0.02 ± 0.88</td>
<td>3.58 ± 1.38***,zz</td>
</tr>
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Table 1: Acute effects of WES on plasma glucose, insulin, and GLP-1 in mice.
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GLP-1 = glucagon-like peptide-1; PPARγ = peroxisome proliferator-activated receptor; PTP 1B = protein tyrosine phosphatase 1B; AMPK = AMP-activated protein kinase

Modified after Habicht et al. 2013
Nerurkar et al. (2008):

- Female C57BL/6 mice were treated with a high fat diet (58.0 kJ% of fat)
- 1.5% of a lyophilized bitter gourd juice added to the diet for 16 weeks

⇒ Lowered body weight and normalized plasma glucose (p<0.05)
⇒ Improved glucose and insulin tolerance
⇒ Enhanced insulin response
Conclusions from *in vitro* and *in vivo* Studies

Studies designed for most significant results

No dietary recommendations are given

Most effective plant part, dosage, preparation has not been defined yet

Anti-diabetic effect of bitter gourd results from a complex action of multiple compounds

⇒ Whole fruit might be better than extracts or isolated compounds

Proven effectiveness of bitter gourd in cell culture and animal studies

⇒ What about human studies?
## Bitter Gourd Human Studies (Habicht et al. 2013)

<table>
<thead>
<tr>
<th>Study subjects</th>
<th>Bitter gourd preparation</th>
<th>Dosage and application</th>
<th>Duration / Design</th>
<th>Study design</th>
<th>Significant (p &lt; 0.05) bitter gourd effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 type I and 8 type II diabetic patients</td>
<td>p-insulin</td>
<td>Subcutaneously, dosage was dependent on blood glucose level</td>
<td>1 dosage</td>
<td>Placebo controlled</td>
<td>Insulin-like effect; decreased blood glucose levels after administration</td>
<td>[2]</td>
</tr>
<tr>
<td>50 type 2 diabetic patients</td>
<td>Dried whole fruit powder pressed to tablets / riboflavin as placebo</td>
<td>6 g per day orally</td>
<td>4 weeks</td>
<td>Randomized single blind placebo controlled</td>
<td>No statistically significant results in regard to fasting plasma glucose, postprandial glucose, or fructosamine levels</td>
<td>[3]</td>
</tr>
<tr>
<td>Diabetic patients (7 patients tested extract / 5 patients tested tablets)</td>
<td>Aqueous extract / fruit powder as tablet</td>
<td>100 mL (extract) or three times a day 5 g (tablet) orally</td>
<td>7 weeks (extract) or 3 weeks (tablet)</td>
<td>Not placebo controlled</td>
<td>Lower postprandial blood glucose levels and lower HbA1c after treatment with bitter gourd extract; no significant effect after treatment with bitter gourd tablets</td>
<td>[4]</td>
</tr>
<tr>
<td>15 type 2 diabetic patients</td>
<td>Methanolic fruit extract</td>
<td>200 mg / day orally in addition to metformin, glibenclamide or both</td>
<td>7 days</td>
<td>Not placebo controlled</td>
<td>Bitter gourd lowered fasting and postprandial glucose levels compared to the drug treatment alone</td>
<td>[5]</td>
</tr>
<tr>
<td>42 patients diagnosed with the metabolic syndrome</td>
<td>Whole fruit powder capsules</td>
<td>4.8 g per day orally</td>
<td>3 months</td>
<td>Open-labeled single-arm study</td>
<td>Decreased incidence rate of metabolic syndrome among study population; lower waist circumference; the trend of increased insulin sensitivity was not significant</td>
<td>[6]</td>
</tr>
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</tr>
<tr>
<td>18 newly diagnosed type 2 diabetic patients without anti-diabetic drugs</td>
<td>Clear juice from the flesh of Sri Lankan bitter gourd variety / distilled water as control</td>
<td>100 mL orally</td>
<td>1 dosage</td>
<td>Not placebo controlled</td>
<td>Improved glucose tolerance in oral tolerance test after bitter gourd treatment; indication for possible non-responders</td>
<td>[7]</td>
</tr>
<tr>
<td>143 newly diagnosed type 2 diabetic patients</td>
<td>Capsules of dried fruit pulp powder or metformin / roasted rice powder and lactose as placebo</td>
<td>500 / 1000 / 2000 mg per day or 1000 mg metformin per day orally</td>
<td>4 weeks</td>
<td>Randomized double blind active controlled, dosage was placebo controlled</td>
<td>2000 mg per day significantly reduced fructosamine levels</td>
<td>[8]</td>
</tr>
<tr>
<td>40 newly diagnosed type 2 diabetic patients or patients with poor blood glucose control</td>
<td>Charantia Ampalaya Capsules© and placebo</td>
<td>3 g per day orally in addition to standard therapy</td>
<td>3 months</td>
<td>Randomized double blind placebo controlled</td>
<td>No statistically significant differences compared to placebo group concerning fasting blood glucose, HbA1c, total cholesterol, or body weight</td>
<td>[9]</td>
</tr>
<tr>
<td>60 type 2 diabetic patients free from serious complications</td>
<td>Mixed powder of bitter gourd fruit, fenugreek seeds, and jambu seeds in either capsule (raw) or biscuit (cooked) form</td>
<td>45 days 1 g per day orally + 45 days 2 g per day orally</td>
<td>90 days</td>
<td>Not placebo controlled</td>
<td>Lower fasting and postprandial blood and urine levels; reduced intake of oral hypoglycemic drugs; raw powder was more effective</td>
<td>[10]</td>
</tr>
<tr>
<td>97 type 2 diabetic patients without insulin treatment</td>
<td>Water soluble bitter gourd extract (Glucokine©) with or without Chromium and Zink supplements</td>
<td>1 g per day orally</td>
<td>4 months</td>
<td>Double-blind placebo controlled</td>
<td>HbA1c dropped significantly after bitter gourd treatment without chromium and zinc supplementation</td>
<td>[11]</td>
</tr>
</tbody>
</table>
Thank you


5) Tongia A, Tongia SK, Dave M. Phytochemical determination and extraction of *Momordica charantia* fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM). Indian J Physiol Pharmacol 2004; 48(2): 241–244


Matsuura H, Asakawa C, Kurimoto M, Mizutani J. α-Glucosidase inhibitor from the seeds of balsam pear (Momordica charantia) and the fruit bodies of Grifola frondosa. Biosci Biotechnol Biochem 2002; 66(7): 1576-1578


Nerurkar PV, Lee YK, Motosue M, Adeli K, Nerurkar VR. *Momordica charantia* (bitter melon) reduces plasma apolipoprotein B-100 and increases hepatic insulin receptor substrate and phosphoinositide-3 kinase interactions. Br J Nutr 2008; 100(4): 751-759