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An Evidence-Based Systematic Review of Gymnema (*Gymnema sylvestre* R. Br.) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review of gymnema (*Gymnema sylvestre* R. Br.), including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Adverse effects, dosing, evidence-based, gymnema (*Gymnema sylvestre* R. Br.), interactions, pharmacodynamics, pharmacokinetics, pharmacology, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to February 2008. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common

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databases) and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, and human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of studies were contacted when clarification was required.

Synonyms/Common Names/Related Substances

- Asclepiadaceae (family), *Asclepias geminata* Roxb., *Gemnema melicida*, GS4 (water-soluble extract of the leaves), gur-mar, gurmar, gurmarbooti, *Gymnema inodum*, *Gymnema montanum*, *Gymnema sylvestre*, kogilam, madhunashini, mangala gymnema, merasingi, meshashringi, meshavalli, miracle plant, periploca of the woods, *Periploca sylvestris*, podapatri, Proβeta, ram's horn, sarkaraikolli, shardunika, sirukurinja, small Indian ipecac, vishani.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Gymnema leaves have been used for more than 2,000 years in India to treat *madhu meha* or "honey urine." It has been used alone and as a component of the Ayurvedic medicinal compound, "Tribang shila," a mixture of tin, lead, zinc, *Gymnema sylvestre* leaves, neem leaves (*Melia azadirachta*), Enicostemma littorale, and jambul seeds (*Eugenia jambolana*).
- Preliminary human evidence suggests that gymnema may be efficacious for the management of serum glucose levels in type 1 and type 2 diabetes, as an adjunct to conventional drug therapy, for up to 20 months. Gymnema appears to lower serum glucose and glycosylated hemoglobin (HbA1c) levels following chronic

use but may not have significant acute effects (Baskaran et al., 1990). Some of the available research has been conducted by authors affiliated with manufacturers of gymnema products. High-quality human trials are lacking in this area (Cicero, Derosa, & Gaddi, 2004; Grover, Yadav, & Vats, 2002; Shapiro & Gong, 2002).

- There is also early evidence suggesting possible efficacy of gymnema as a lipid-lowering agent. Gymnema was shown in one study to possess antimicrobial action against *Bacillis pumilis*, *B. subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* but not against *E. coli* and *Proteus vulgaris* (Satdive, Abhilash, & Fulzele, 2003).
- One of the major side effects or actions of gymnema is taste alteration. Studies have shown that gymnema reduces the perception of sweetness inside the mouth and seems to increase the perception of bitterness by neural inhibition (Brala & Hagen, 1983; Lawless, 1979; Meiselman & Halperin, 1970; Meiselman & Halpern, 1970; Min & Sakamoto, 1998; Simons, O'Mahony, & Carstens, 2002; Warren, Warren, & Weninger, 1969).

Scientific Evidence

Type 1 diabetes mellitus	B
Type 2 diabetes mellitus	B

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.

Level of Evidence Grade	Criteria
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e. lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.
†Listed separately in the "Historical or Theoretical Uses That Lack Sufficient Evidence" section.

Historical or Theoretical Uses That Lack Sufficient Evidence

- Allergy, antioxidant, antimicrobial (Satdive et al., 2003), aphrodisiac, cancer, cardiovascular disease, constipation, cough, dental caries, digestive stimulant, diuresis, gout (Shimizu et al., 1997), hepatoprotection, hypertension (Preuss et al., 1995, 1998), laxative, liver disease, malaria, metabolic disorders, obesity, rheumatoid arthritis (Shimizu et al., 1997), snake venom antidote (Kothe & Uppal, 1997), stomach ailments, uterine stimulant, viral infection.

Expert Opinion and Historic/Folkloric Precedent

- Gymnema leaves have been used for more than 2,000 years in India to treat *madhu meha* or "honey urine." It has been used alone and as a component of the Ayurvedic medicinal compound, "Tribang shila," a mixture of tin, lead, zinc, *Gymnema sylvestre* leaves, neem leaves (*Melia azadirachta*), Enicostemma littorale, and jambul seeds (*Eugenia jambolana*). Traditional healers observed that chewing the leaves of gymnema resulted in a reversible loss of sweet-taste perception.
- The plant has also been used in African healing traditions; for example, Tanzanian healers used it as an aphrodisiac. Other traditional applications include use as an antimalarial agent, digestive stimulant, laxative, diuretic, and snake venom antidote.

Brief Safety Summary

- *Possibly unsafe*: When used in patients taking other hypoglycemic agents, because of possible potentiation of effects. Hypoglycemic effects associated with gymnema have been noted in both diabetic and nondiabetic individuals (Khare, Tondon, & Tewari, 1983). When used in patients taking weight loss agents because there may be a potential for additive effects (Preuss et al., 2005).

DOSING/TOXICOLOGY

General

- Listed doses are based on those most commonly used in available trials, on historical practice, or on manufacturer recommendations. However, with natural products, it is often not clear what the optimal doses are to balance efficacy and safety.

Preparation of products may vary from manufacturer-to-manufacturer and from batch-to-batch within one manufacturer. Because it is often not clear what the active components of a product are, standardization may not be possible and the clinical effects of different brands may not be comparable.

Standardization

- At least one manufacturer offers an extract of gymnema standardized to 25% gymnemic acid, but this extract has not yet been clinically evaluated.
- An ethanolic acid-precipitated extract from gymnema, labeled GS4, has been used in human trials (Baskaran et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990). GS4 has since been patented as the product Proβeta, by a research team who has conducted some of the research in this area. According to the makers of Proβeta, the preparation is standardized to possess a specific biological result, as measured by a test developed by the company that evaluates "pancreotropic" effects.
- Examples of other standardized commercially available products include Beta Fast GXR (Informulab, Omaha, NE, USA), 400 mg standardized to 25% gymnemic acids; Gymnesyl (Nature's Herbs, Twinlab, American Fork, UT, USA), extract standardized for 150 mg of crude gymnemic acids; and Gymnema (Nature's Way, Lehi, UT, USA), 260 mg standardized to 75% gymnemic acids.

Dosing

Adult (age ≥18)

Oral

- *Hyperlipidemia*: In one study, patients with type 2 diabetes mellitus received 400 mg of gymnema extract for 18–20 months (Baskaran et al., 1990).
- *Type 1 diabetes*: GS4 (200 mg) has been taken orally, twice daily (Shanmugasundaram, Rajeswari, et al., 1990), under careful continuation of insulin. Doses of insulin or other concomitant hypoglycemic drugs may have to be adjusted or discontinued under the supervision of a healthcare professional.
- *Type 2 diabetes*: GS4 (200 mg) has been taken orally, twice daily (Baskaran et al., 1990), or 2 ml of an aqueous decoction (10 g shade-dried powdered leaves per 100 ml), three times daily (Khare et al., 1983). Doses of insulin or other concomitant hypoglycemic drugs may have to be adjusted or discontinued under the supervision of a healthcare professional. Six to fifteen drops of *Gymnema sylvestre* "Q" with 1/4 cup of water has been taken two to four times daily for 6 months (Kothe & Uppal, 1997).
- *Weight loss*: *Gymnema sylvestre* extract (GSE; 400 mg) has been studied in combination with a water-soluble, calcium-potassium salt of (−)-hydroxycitric acid (HCA-SX) (4,667 mg), and niacin-bound chromium (NBC; 4 mg) (Preuss et al., 2005).
- *Note*: The manufacturer PharmaTerra recommends the dose for their product Proβeta (GS4) to be two 250 mg capsules taken twice daily at mealtimes (for adults weighing >100 pounds) or one 250 mg capsule taken twice daily at mealtimes (for adults weighing <100 pounds).

Children (age <18)

- Insufficient available evidence.

Toxicology

- Insufficient available evidence.

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

- There is a lack of allergy/hypersensitivity to gymnema reported in the available literature. In theory, allergic cross-reactivity may occur to members of the Asclepiadaceae (milkweed) family.

Adverse Effects

- *General*: Aside from hypoglycemia and potentiation of the effects of hypoglycemic drugs following chronic use of gymnema, no clinically significant adverse effects have been associated with oral gymnema in the available literature, in studies up to 20 months in duration.
- *Endocrine*: Multiple animal studies have reported hypoglycemic effects associated with ingestion of gymnema leaves. Gymnema reduced hyperglycemia in experimentally and spontaneously diabetic rats and rabbits (Chattopadhyay, 1998; Gupta & Variyar, 1964; Okabayashi et al., 1990; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995), as well as in normal and diabetic humans (Baskaran et al., 1990; Khare et al., 1983; Kothe & Uppal, 1997; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990). One subject with brittle diabetes had to discontinue gymnema in a clinical trial due to repeated hypoglycemic episodes (Shanmugasundaram, Rajeswari, et al., 1990). Hypoglycemic effects have been noted in both diabetic and nondiabetic individuals (Khare et al., 1983).
- *Oral (taste effects)*: Gymnema has been reported to possess a sweet-taste-suppressing effect, attributed to the peptide gurmarin (Brala & Hagen, 1983; Imoto et al., 1991; Kamei et al., 1992; Koch, Desaiah, & Cutkomp, 1973; Lawless, 1979). Historically, this phenomenon has been observed, prompting the Hindi name *gurmar* or "sugar destroyer."

Precautions/Warnings/Contraindications

- Use cautiously in diabetic patients using hypoglycemic medications, due to possible potentiation of effects. Serum glucose levels should be monitored, and doses of concomitant hypoglycemic drugs may require adjustment under the supervision of a healthcare professional. Hypoglycemia may also occur in nondiabetic patients (Khare et al., 1983).
- Use cautiously in patients taking weight loss agents because there may be a potential for additive affects. GSE has been used in combination with other weight loss agents (hydroxycitric acid and NBC), although a mechanism of action is unclear (Preuss et al., 2005).

- Use cautiously in patients taking antilipemic agents because there may be a potential for additive effects. Reductions in levels of serum triglycerides, total cholesterol, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) have been observed in animals following administration of gymnema (Bishayee & Chatterjee, 1994; Terasawa, Miyoshi, & Imoto, 1994).

Pregnancy and Lactation

- Not recommended due to insufficient available safety information.

INTERACTIONS

Gymnema/Drug Interactions

- *Antidiabetic agents*: Gymnema may potentiate the effects of hypoglycemic drugs in diabetic patients (Baskaran et al., 1990; Shanmugasundaram, Gopinath, et al., 1990a; Shanmugasundaram, Rajeswari, et al., 1990). Doses of such medications may therefore need adjustment. Serum glucose levels should be monitored, and doses of concomitant hypoglycemic drugs may require adjustment under the supervision of a healthcare professional. Multiple animal studies have reported hypoglycemic effects associated with the ingestion of gymnema leaves. Gymnema reduced hyperglycemia in experimentally and spontaneously diabetic rats and rabbits (Chattopadhyay, 1998; Gupta & Variyar, 1964; Okabayashi et al., 1990; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995), as well as in normal and diabetic humans (Baskaran et al., 1990; Khare et al., 1983; Kothe & Uppal, 1997; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990).
- *Antilipemic agents*: Reductions in levels of serum triglycerides, total cholesterol, VLDL, and LDL have been observed in animals following administration of gymnema (Bishayee & Chatterjee, 1994; Terasawa et al., 1994). A study of gymnema in type 2 diabetes patients reported decreased cholesterol and triglyceride levels as a secondary outcome (Baskaran et al., 1990). Concomitant use of gymnema with other lipid-lowering agents may potentiate these effects.
- *Antiobesity agents*: Human study has investigated GSE (400 mg) in combination with other agents for obesity, although a mechanism of action is unclear (Preuss et al., 2005).

Gymnema/Herb/Supplement Interactions

- *Antilipemics*: Reductions in levels of serum triglycerides, total cholesterol, VLDL, and LDL have been observed in animals following administration of gymnema (Bishayee & Chatterjee, 1994; Terasawa et al., 1994). A study of gymnema in type 2 diabetes patients reported decreased cholesterol and triglyceride levels as a secondary outcome (Baskaran et al., 1990). Concomitant use of gymnema with other lipid-lowering agents may potentiate these effects.
- *Antiobesity herbs and supplements*: Human study has investigated GSE (400 mg) in combination with other agents for obesity, although a mechanism of action is unclear (Preuss et al., 2005).

- *Appetite suppressants*: Human study has investigated GSE (400 mg) in combination with other agents for obesity, although a mechanism of action is unclear (Preuss et al., 2005).
- *Chromium*: Human study has investigated GSE (400 mg) in combination with niacin bound chromium, although a mechanism of action is unclear (Preuss et al., 2005).
- *Fat-soluble vitamins*: In an animal study, absorption of oleic acid (a fatty acid) was decreased by gymnema (Wang et al., 1998). It is unknown whether gymnema exerts these effects in humans or affects the absorption of other nutritionally important lipids or fat-soluble vitamins (A, D, E, K).
- *Garcinia*: Human study has investigated GSE (400 mg) in combination with hydroxycitric acid, a component of garcinia (Preuss et al., 2005).
- *Hypoglycemics*: Gymnema may potentiate the effects of hypoglycemic herbs or supplements in diabetic patients (Baskaran et al., 1990; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990). Doses of these agents may therefore need adjustment. Serum glucose levels should be monitored, and doses of concomitant hypoglycemic agents may require adjustment under the supervision of a healthcare professional. Multiple animal studies have reported hypoglycemic effects associated with ingestion of gymnema leaves. Gymnema reduced hyperglycemia in experimentally and spontaneously diabetic rats and rabbits (Chattopadhyay, 1998; Gupta & Variyar, 1964; Okabayashi et al., 1990; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995), as well as in normal and diabetic humans (Baskaran et al., 1990; Khare et al., 1983; Kothe & Uppal, 1997; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990).

Gymnema/Food Interactions

- *Fatty foods*: In an animal study, absorption of oleic acid (a fatty acid) was decreased by gymnema (Wang et al., 1998). It is unknown whether gymnema exerts these effects in humans or affects the absorption of other nutritionally important lipids or fat-soluble vitamins (A, D, E, K).

Gymnema/Lab Interactions

- *Blood glucose, glycosylated hemoglobin (HbA1c)*: On the basis of animal research and preliminary human data, ingestion of gymnema may cause hypoglycemia in diabetic patients and reductions over time in HbA1c levels (Baskaran et al., 1990; Chattopadhyay, 1998; Gupta & Variyar, 1964; Khare et al., 1983; Kothe & Uppal, 1997; Okabayashi et al., 1990; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995). Hypoglycemic effects have been noted in patients without diabetes as well as in patients with diabetes (Khare et al., 1983).
- *Lipid panel*: In a small human study, patients with type 2 diabetes taking gymnema in addition to oral hypoglycemic drugs experienced reductions in cholesterol, triglycerides, and free fatty acids, while subjects taking oral hypoglycemic agents alone did not (Baskaran et al., 1990). Serum triglycerides, total cholesterol,

VLDL, and LDL cholesterol-lowering effects have been observed in animals (Bishayee & Chatterjee, 1994; Terasawa et al., 1994). The mechanism of this effect may be via decreased cholesterol synthesis, increased cholesterol metabolism, or decreased fat absorption (Wang et al., 1998).

MECHANISM OF ACTION

Pharmacology

- *Constituents*: Few studies have closely evaluated the constituents of *Gymnema sylvestre* leaf. Proposed active components include gurmarin, conduritol A, and triterpene glycosides (Persaud, Al Majed, Raman, & Jones, 1999; Sinsheimer, Rao, & McIlhenny, 1970; Yoshikawa et al., 1997). Gymnemoside b (Yoshikawa et al., 1997) and gymnema acid V and VII appear to be the key saponin constituents (Murakami et al., 1996).
- *Antimicrobial effects*: In one study, gymnema was shown to possess antimicrobial action against *Bacillis pumilis*, *B. subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* but not against *E. coli* and *Proteus vulgaris* (Satdive et al., 2003).
- *Hypoglycemic effects*: Multiple animal studies have reported hypoglycemic effects associated with the ingestion of gymnema leaves. Gymnema reduced hyperglycemia in experimentally and spontaneously diabetic rats and rabbits (Chattopadhyay, 1998; Gupta & Variyar, 1964; Okabayashi et al., 1990; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995), as well as in normal and diabetic humans (Ananthan, Baskar, et al., 2003; Ananthan, Latha, et al., 2003; Baskaran et al., 1990; Gholap & Kar, 2003; Jiang, 2003; Khare et al., 1983; Kothe & Uppal, 1997; Porchezhian & Dobriyal, 2003; Satdive et al., 2003; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Xie et al., 2003). Gymnema may act by enhancing insulin secretion through increased pancreatic β-cell number and improved cell function (Preuss et al., 1998; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990). However, insulin resistance was not improved by gymnema in one animal model of diabetes (Tominaga et al., 1995). Other proposed mechanisms include stimulation of the release of endogenous insulin (Baskaran et al., 1990; Persaud et al., 1999) via interactions with insulinotropic enteric hormones or increases in glucose utilization (Shanmugasundaram et al., 1983). Such activities may explain the observed hypoglycemic effects in type 2 diabetics. Gymnema has also been reported to restore levels of glycoproteins in diabetic rats to normal, thereby potentially preventing diabetic microangiopathy and other pathological organ changes (Rathi, Visvanathan, & Shanmugasundaram, 1981).
- *Lipid effects*: Serum triglycerides, total cholesterol, VLDL, and LDL cholesterol-lowering effects have been observed in animals (Bishayee & Chatterjee, 1994; Terasawa et al., 1994). The mechanism may by via a decrease in the synthesis or increase in the metabolism of cholesterol, or through decreased intestinal fat absorption (Wang et al., 1998).
- *Taste effects*: Gymnema has been reported to possess a sweet-taste-suppressing effect, attributed to the peptide gurmarin (Brala & Hagen, 1983; Imoto et al.,

1991; Kamei et al., 1992). This effect may result from interference with Na+/K+ ATPase activity of taste receptors (Koch et al., 1973) or from neural inhibition (Lawless, 1979). Historically, this phenomenon has been observed, prompting the Hindi name *gurmar* or "sugar destroyer."
- Saponin I and the sodium salt of alternoside II (4) from gymnema exhibited antisweet activity (Ye, Liu, Zhang, Che, & Zhao, 2001).
- *Weight loss effects*: Human study has investigated GSE (400 mg) in combination with other agents for weight loss; however, the exact mechanism of action involving gymnema is unclear (Preuss et al., 2005).

Pharmacodynamics/Kinetics

- *Absorption*: In one small human study, it was reported that oral administration of gymnema did not have acute effects on fasting serum glucose levels (after 45 min; Baskaran et al., 1990)

HISTORY

- *Gymnema sylvestre* is a woody, climbing plant native to India. The leaves are most commonly used medicinally, although the stem is also believed to possess some pharmacological action. The leaves have been used for over 2,000 years in India to treat madhu meha or "honey urine." Chewing the leaves was noted to diminish the ability to discriminate sweet tastes, which along with hypoglycemic properties may have prompted the Hindi name *gurmar* or "sugar destroyer." Gymnema has a long history of use in individuals with diabetes.
- Extracts of gymnema are widely used in Australian, Japanese, Vietnamese, and Indian folk medicine. Gymnema preparations modulate taste, particularly suppressing sweet taste sensations, and are used in the treatment of diabetes mellitus and in food additives against obesity and caries. Gymnema has become a popular natural product used in the management of blood sugar levels in individuals with diabetes and is believed by some to play a role in reducing serum lipids (Porchezhian & Dobriyal, 2003).

EVIDENCE TABLE

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include the following:

- *Randomized controlled trial (RCT)*: An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed.

Condition Treated (Primary or Secondary Outcome)	Evidence/Study Type	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit (How Strong is the Effect?)	Absolute Risk Reduction	Number of Patients Needed to Treat for One Outcome	Comments
Type 1 diabetes	Controlled trial, nonrandomized, nonblinded	Shanmugasundaram, Rajeswari, et al., 1990	64	Yes	0	Large	59%	2	GS4 (gymnema) plus insulin vs. insulin alone, 11 dropouts, 40 nondiabetics also studied, author affiliated with manufacturer.
Type 2 diabetes	Before and after study, nonrandomized, nonblinded	Baskaran et al., 1990	47	Yes	1	Large	23%	4	GS4 (gymnema) added to oral hypoglycemic drugs improved fasting glucose and HbA1c levels.
Type 2 diabetes	Case series	Kothe & Uppal, 1997	21	NA	0	NA	NA	NA	Gymnema administered over 6-month period, uncontrolled, limited reporting of numerical results.
Type 2 diabetes	Case series	Khare et al., 1983	16	Yes	0	Large	NA	NA	10 days of gymnema reduced serum glucose levels in both diabetic and nondiabetic patients.

Explanation of columns in Natural Standard EVIDENCE TABLE

1	2	3	4	5	6	7	8	9	10
Condition	Study design	Author, year	*N*	Statistically significant?	Quality of study 0–2 = poor 3–4 = good 5 = excellent	Magnitude of benefit	Absolute risk reduction	Number needed to treat	Comments

True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.

- *Equivalence trial*: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care and may not include a placebo arm.
- *Before and after comparison*: A study that reports only the change in outcome in each group of a study and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- *Case series*: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- *Case-control study*: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.
- *Cohort study*: A study which assembles a group of patients with certain baseline characteristics (e.g., use of a drug) and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.
- *Meta-analysis*: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study-to-study, hindering direct comparison.
- *Review*: An author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- *Systematic review*: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically Significant?

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as p values). P = pending verification.

Quality of Study

- A numerical score between 0–5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad score calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:

- Large: if >1 SD
- Medium: if 0.5 to 0.9 SD
- Small: if 0.2 to 0.4 SD
- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by

subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = [Mean Treatment − Mean Placebo]/SDp).

Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate – experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. P = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the Absolute Risk Reduction into 1 (1/ARR). P = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/sub-groups (age, gender, etc.). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

Type 1 Diabetes Mellitus

- *Summary*: Multiple animal studies have noted gymnema to lower serum glucose levels (Ananthan, Baskar, et al., 2003; Ananthan, Latha, et al., 2003; Chattopadhyay, 1998; Gholap & Kar, 2003; Gupta & Variyar, 1964; Jiang, 2003; Okabayashi et al., 1990; Porchezhian & Dobriyal, 2003; Satdive et al., 2003; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985;; Tominaga et al., 1995; Xie et al., 2003). Preliminary evidence from small, methodologically flawed human trials suggest hypoglycemic effects of chronic oral gymnema when used in patients with type 1 or type 2 diabetes, as an adjunct to insulin or oral hypoglycemic drugs. The onset of effect has not been clearly described, although one study noted that oral administration of gymnema did not have acute effects on fasting serum glucose levels (after 45 min; Baskaran et al., 1990). The available studies

have assessed the effects of gymnema after 10 days, up to 20 months. Although it appears that gymnema may act to lower serum glucose levels, further studies of dosing, safety, and efficacy are merited before a strong recommendation can be made. Multiple drugs are available that have been demonstrated to establish good long-term control of blood glucose levels, and gymnema has not been thoroughly evaluated as a safe or effective alternative or adjunct to these agents.

- *Evidence*: Shanmugasundaram et al. conducted a study in 64 individuals with type 1 diabetes (Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990). All subjects were continued on insulin therapy during the trial, and 27 patients were concurrently started on 200 mg of GS4 twice daily (an ethanolic acid-precipitated extract of gymnema). Outcomes measures included fasting glucose levels, HbA1c levels, and insulin requirements. The gymnema subjects were followed for a period, which varied, from 6 to 30 months, while the 37 insulin-only controls were tracked for 10–12 months. Eleven subjects dropped out during the initial 6 months (10 for nonmedical reasons, one for brittle diabetes). In the gymnema group, mean insulin requirements were reduced by 50%, accompanied by significant reductions in mean fasting blood glucose levels, from 232 mg/dl to 152 mg/dl. HbA1c levels were also reportedly reduced. The insulin-only group exhibited no significant mean decreases in insulin requirements or blood sugar levels. Subjective measures of well being (alertness, work, and school performance) were also reported to improve with gymnema therapy. A secondary outcome of C-peptide level was measured in the two groups and compared with values for 40 nondiabetic individuals. A statistically significant lower mean C-peptide value was found in the gymnema plus insulin group (0.185) versus insulin alone (0.272) but was higher than the mean value in nondiabetics (0.105). During the study, no adverse effects besides hypoglycemia were observed. Although these results are promising, the lack of blinding allows for the possible introduction of bias, and the lack of randomization may allow for the influence of confounding factors. Baseline patient characteristics and statistical analysis were not well described. The principal author is involved with a company that produces a GS4 product.

Type 2 Diabetes Mellitus

- *Summary*: Multiple animal studies have noted gymnema to lower serum glucose levels (Ananthan, Baskar, et al., 2003; Ananthan, Latha, et al., 2003; Chattopadhyay, 1998; Gholap & Kar, 2003; Gupta & Variyar, 1964; Jiang, 2003; Okabayashi et al., 1990; Porchezhian & Dobriyal, 2003; Satdive et al., 2003; Shanmugasundaram et al., 1983; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990; Srivastava et al., 1985; Tominaga et al., 1995; Xie et al., 2003). Preliminary evidence from small, methodologically flawed human trials suggest hypoglycemic effects of chronic oral gymnema when used in patients with type 1 or type 2 diabetes, as an adjunct to insulin or oral hypoglycemic drugs. The onset of effect has not been clearly described, although one study noted that oral administration of gymnema did not have acute effects on fasting serum glucose levels (after 45 min; Baskaran et al., 1990). The available studies have assessed effects of gymnema after 10 days, up to 20 months. Although

it appears that gymnema may act to lower serum glucose levels, further studies of dosing, safety, and efficacy are merited before a strong recommendation can be made. Multiple drugs are available that have been demonstrated to establish good long-term control of blood glucose levels, and gymnema has not been thoroughly evaluated as a safe or effective alternative or adjunct to these agents.

- *Evidence*: Baskaran et al. performed a controlled, nonrandomized, nonblinded study in 47 patients with type 2 diabetes (Baskaran et al., 1990). GS4 extract (400 mg daily) was administered for 18–20 months to 22 patients, in addition to baseline conventional oral hypoglycemic agents. The control group remained on conventional drug therapy alone without GS4 and was followed for 12 months. After 18–20 months, in the gymnema group, fasting glucose levels were reported to be 29% lower than baseline ($p < .001$), and mean HbA1c levels decreased from a baseline value of 11.91%–8.48% ($p < .001$). Insulin responses ware reported as being superior in the gymnema-supplemented group ($p < .01$). Five subjects in the gymnema group were able to discontinue hypoglycemic medications. No significant changes in glucose or HbA1c levels were observed in patients continued on oral hypoglycemic medications alone after 8–10 months. As a secondary outcome, blood lipid levels were evaluated. In the GS4 group, there were significant reductions in plasma lipid levels, including cholesterol, triglycerides, and free fatty acids, while lipid levels in patients on conventional drug therapy alone remained elevated. Methodological limitations of this study include the lack of randomization or blinding. Glucose and HbA1c levels were compared with baseline values in each group, rather than compared between groups, making this a "before-and-after" study design (a methodologically weaker design than a between-group comparison).
- A briefly described case series by Kothe and Uppal examined the use of gymnema in 21 subjects with type 2 diabetes over a 6-month period (Kothe & Uppal, 1997). This paper was presented at the Scientific Session of the 9th Annual International Homeopathic Conference of the Asian Homeopathic Medical League, Jaipur, India. All subjects received 6–15 drops of *Gymnema sylvestre* "Q" with 1/4 cup of water, taken two to four times daily, on a sliding scale based on blood sugar measurements. Additional homeopathic remedies were allowed in "complicated" cases. The authors reported that 16 of 21 patients demonstrated "moderate" to "excellent" blood glucose control. Although suggestive, the lack of a control group and vague description of baseline patient characteristics raises questions about whether these results were due to the natural course of disease, rather than a result of gymnema therapy. Details were not provided regarding methodology or data analysis, and glucose levels during the study period were provided only for two patients. Results may have been confounded by the use of additional homeopathic remedies in some patients, which were not described.
- In a 10-day study described in a letter to the editor, Khare et al. investigated the effects of gymnema on glucose levels in 10 healthy young adults (ages 19–25) and 6 diabetic adults (age 35–50) with mild-to-moderate baseline hyperglycemia, but without diagnosed diabetic complications (Khare et al., 1983). Subjects were not receiving diabetes treatment prior to the trial. Glucose tolerance tests were performed before and after administration of gymnema (2 g, three times daily

of a 10 g/100 ml aqueous decoction of shade-dried powdered leaves). Administration of gymnema for 10 days significantly reduced fasting blood sugar levels compared with baseline in both normal and diabetic subjects and significantly reduced mean glucose levels in diabetics after oral glucose load at both 30 min (110.7 mg/dl vs. 135.7 mg/dl) and 120 min (180.7 mg/dl vs. 220.0 mg/dl). As a case series, this study lacked comparison to controls receiving placebo or a comparison agent. Methodology and statistical analysis were not well described in this brief publication.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Proβeta (PharmaTerra, Inc., Bellevue, WA): A patented ethanolic acid-precipitated extract from gymnema, also called GS4. According to the makers of Proβeta, the preparation is standardized to possess a specific biological result, as measured by a test developed by the company, which evaluates "pancreotropic" effects (Baskaran et al., 1990; Shanmugasundaram, Gopinath, et al., 1990; Shanmugasundaram, Rajeswari, et al., 1990).
- Beta Fast GXR (Informulab, Omaha, NE, USA), 400 mg standardized to 25% gymnemic acids; Gymnesyl (Nature's Herbs, Twinlab, American Fork, UT, USA), extract standardized for 150 mg of crude gymnemic acids; Gymnema (Nature's Way, Lehi, UT, USA), 260 mg standardized to 75% gymnemic acids.

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