Gymnema

Gymnema sylvestre

Nome botanico

Gymnema sylvestre (Retz.) *R.* Br. ex Schult. *(Asclepiadaceae)*

Parti usate

Foglie.

Componenti principali

Acidi gymnemici (acido gymnemico e deacilgymnemico), gymnemagenine, gymnemasine, gurmarina.

Attività farmacologica

Attività ipoglicemizzante. Riduzione della percezione del gusto dolce.

Impiego clinico

Trattamento coadiuvante del diabete mellito non insulino-dipendente, anche associato a condizioni di sovrappeso e obesità.

Controindicazioni

Nessuna controindicazione nota.

Avvertenze e speciali precauzioni d'uso

Non sono noti studi clinici controllati in donne in gravidanza e durante l'allattamento, in conformità con la prassi medica generale, il prodotto non deve essere utilizzato senza prima aver sentito il parere del medico.

Interazioni

La *Gymenma sylvestre* può potenziare l'azione degli ipoglicemizzanti orali e dell'insulina; se si stanno assumendo tali farmaci consultare il medico prima di assumere il prodotto.

Effetti indesiderati

Nessuno degno di nota.

Note Bibliografiche

Composizione

Nel fitocomplesso di *Gymnema sylvestre* sono stati identificati vari componenti: nove differenti acidi gymnemici dalla nota attività ipoglicemizzante[1,2], fra i quali l'acido gymnemico e l'acido deacilgymnemico[3,4]; le saponine degli acidi gymnemici[5]; le gymnemagenine; altre quattro saponine triterpeniche, identificate come gymnemasine A, B, C e D[6]; un polipeptide ad attività anti-dolcificante,

[1] "Three certified preparations of dried extracts of Gymnema sylvestre with gravimetric concentrations of "25%," "50%," and "75%" were studied. After extraction with a water-alcohol mixture, the supernatants of all preparations were analyzed for the presence of phenolic acids and amino acids by ascending thin-layer chromatography. The samples were found to contain significant quantities of a diversity of organic compounds, including plant phenols. The presence of the latter was supported by the reaction with iron (III) chloride and the Pauli diazo reaction. The ninhydrin reaction showed that the samples contained some quantities of amino acids. These were greatest in the 50% preparation (0.15 mol/kg). **Gymnema sylvestre was found to contain an interesting amino acid composition, in that there was no proline**. According to the certification, **the molar concentration of gymnemic acids in properties was 0.12 mol/kg, which was consistent with the concentrations of phenolic acids and amino acids identified in the present studies**. Thus, purification of dry extracts of Gymnema sylvestre to obtain pure preparations of gymnemic acids requires procedures to reduce the contents of satellite compounds." *(Khramov VA, Spasov A A, Samokhina MP. Chemical composition of dry extracts of Gymnema sylvestre leaves. Pharmaceutical Chemistry Journal 2008; Vol. 42, No. 1, p.29-31. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 42, No. 1, pp. 30 – 32, January, 2008).*

[2] "**Investigation of hypoglycemic activity of major saponin constituents from "gymnemic acid"**… exposed not only two new saponins, gymnemosides a (1) and b (2), but also gymnemoside b and gymnemic acid V (7) as active principles. Furthermore, an acetyl group linked 16- or 22-hydroxy group in 1 and 2 was found to migrate easily to primary 28-hydroxyl group, while acyl migration from 28-hydroxy group in 3 was little observed." *(Murakami N, Murakami T, Kadoya M, Matsuda H, Yamahara J, Yoshikawa M. New hypoglycemic constituents in "gymnemic acid" from Gymnema sylvestre. Chem Pharm Bull 1996; 44: 469-71).*

[3] "**The phyto-constituents of Gymnema sylvestre are used in the treatment of diabetes and obesity**. The present work reports on the **extraction of gymnemic acid** through gymnemagenin from callus cultures of G. sylvestre. Components were separated on pre-coated silica gel 60 GF254 plates with chloroform:methanol (8:2) and scanned using a densitometric scanner at 205 nm in the near-UV region. Linearity of determination of gymnemagenin was observed in the range 2-10 microg. The average percentage recovery of gymnemagenin from leaf callus extracts was 98.9+/-0.3." *(Murakami (Kanetkar PV, Singhal RS, Laddha KS, Kamat MY. Extraction and quantification of gymnemic acids through gymnemagenin from callus cultures of Gymnema sylvestre. Phytochem Anal. 2006 Nov;17(6):409-13).*

[4] *Suzuki K, Ishihara S, Uchida M, Komoda Y. Quantitative analysis of deacylgymnemic acid by high-performance liquid chromatography. Yakugaku Zasshi 1993; 113:316-20.*

[5] "**Two new oleanane-type triterpenoid saponins, gymnemoside-W1 and W2, together with seven known compounds were isolated from the leaves of Gymnema sylvestre R. Br**. By means of spectral and chemical analysis, the structures of the new compounds were elucidated as 16 beta-hydroxyl olean-12-en-3-O-[beta-D-glucopyranosyl (1-->6)-beta-D-glucopyranosyl]-28-O-beta-D-glucopyranoside(1) and 16 beta,21 beta,28-trihydroxyl-olean-12-ene-3-O-glucoronopyranoside (2). The EtOH/H(2) O extracts of this plant were shown to be able to inhibit glucose absorption in rats." *(Zhu XM, Xie P, Di YT, Peng SL, Ding LS, Wang MK. Two new triterpenoid saponins from Gymnema sylvestre. J Integr Plant Biol. 2008 May;50(5):589-92).*

[6] *Sahu NP, Mahato SB, Sarkar SK, Poddar G. Triterpenoid saponins from Gymnema sylvestre. Phytochemistry 1996; 41: 1181-5.*

la gurmarina[7]. Inoltre, conduritolo A (tetraossicicloesene)[8], fitosteroli, pectine.

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche ed i più noti impieghi clinici descritti per la *Gymnema sylvestre* sono:

Medicina popolare. Le foglie, dal caratteristico sapore amaro e acre, vengono impiegate da oltre 2000 anni nella medicina ayurvedica per il trattamento della cosiddetta "urina dolce", ora nota come diabete mellito. Fra gli abitanti di Bombay e di Gujarat esisteva l'usanza di masticare le foglie fresche per ridurre la glicosuria (Madhumeha). Il nome stesso della droga deriva dal termine "Gur mar" che in lingua Hindu vuol dire letteralmente "mangia zucchero". Inoltre, nella medicina tradizionale indiana le preparazioni di foglie di Gymnema prevengono e curano le malattie degli occhi legate a opacizzazione del cristallino, della cornea e del corpo vitreo (cataratta ecc.), sono un buon rimedio nei disturbi cardiaci e nelle emorroidi.

Attività antidiabetica. La *Gymnema sylvestre* è un fitocomplesso utilizzato con successo nel trattamento del diabete mellito non-insulino dipendente (NIDDM), sia singolarmente[9] che in associazione ad altri fitocomplessi[10]. La potenziale efficacia clinica della droga sul diabete di tipo II è stata recentemente riconosciuta anche dall'associazione americana dei medici di medicina generale[11]. Sebbene l'esatto meccanismo dell'azione ipoglicemizzante della pianta non sia ancora

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7 *Kamei K, Takano R, Miyasaka A, Imoto T, Hara S. Amino acid sequence of sweet-taste-suppressing peptide (gurmarin) from the leaves of Gymnema sylvestre. J Biochem 1992; 111: 109-12.*

8 "To study on the chemical constituents from the stem of Gymnema sylvestre, the constituents were extracted by percolation with ethanol. Then the extract was separated by systemic solvent separation methods. The part of n-butanol extract was isolated and purified by macroporous adsorptive resins, silica gel column chromatography, sephadex gel column chromatography and recrystallization. The isolated compounds were identified by spectrum methods. Results: **Eight compounds were isolated and identified as fallows: Conduritol A(I), 1-Heptadecanol(II), Stigmasterol glucoside(III), 1-Quercitol(IV), 1-Octadecanol(V), Potassium nitrate(VI), Lupeol cinnamate(VII), Stigmasterol(VIII)**. Conclusion: Chemical compounds II, III, V, VII are firstly obtained from this plant." *(Zhen HS, Zhu XY, Lu RM, Liang J, Qiu Q, Meng QM. Research on chemical constituents from stem of Gymnema sylvestre. Zhong Yao Cai. 2008 Aug;31(8):1154-6).*

9 *Leach MJ. Gymnema sylvestre for diabetes mellitus: a systematic review. J Altern Complement Med. 2007 Nov;13(9):977-83.*

10 "Present investigation was undertaken to evaluate antihyperglycemic, antihyperlipidemic and antioxidant activities of **Dihar, a polyherbal formulation containing drugs from eight different herbs** viz., Syzygium cumini, Momordica charantia, Emblica officinalis, **Gymnema sylvestre**, Enicostemma littorale, Azadirachta indica, Tinospora cordifolia and Curcuma longa in streptozotocin (STZ, 45 mg/kg iv single dose) induced type 1 diabetic rats. STZ produced a significant increase in serum glucose, cholesterol, triglyceride, very low density lipoprotein, low density lipoprotein, creatinine, and urea levels in diabetic rat. Treatment with Dihar (100 mg/kg) for 6 weeks produced decrease in STZ induced serum glucose and lipids levels and increased insulin levels as compared to control. Dihar produced significant decrease in serum creatinine and urea levels in diabetic rats. There was a significant decrease in reduced glutathione, superoxide dismutase, catalase levels and increase in thiobarbituiric acid reactive species levels in the liver of STZ-induced diabetic rats. **Administration of Dihar to diabetic rats significantly reduced the levels of lipid paroxidation and increased the activities of antioxidant enzymes. The results suggest Dihar to be beneficial for the treatment of type 1 diabetes**." *(Patel SS, Shah RS, Goyal RK. Antihyperglycemic, antihyperlipidemic and antioxidant effects of Dihar, a polyherbal ayurvedic formulation in streptozotocin induced diabetic rats. Indian J Exp Biol. 2009 Jul;47(7):564-70).*

11 "To review clinical evidence supporting complementary and alternative medicine interventions for improving glycemic

completamente noto, esso sembra essere per certi aspetti simile a quello dei farmaci ipoglicemizzanti orali della classe delle sulfaniluree, che stimolano la secrezione insulinica da parte delle beta-cellule pancreatiche. I principi attivi della droga sono in effetti in grado di stimolare la secrezione pancreatica di insulina[12], nonché il numero e la funzionalità delle cellule beta, ed inoltre possono favorire la captazione e l'utilizzazione tissutale di glucosio[13].

Le sulfaniluree stimolano la secrezione insulinica da parte delle beta-cellule pancreatiche, per cui è necessaria una residua integrità del pancreas perché si abbia l'effetto ipoglicemizzante: gli effetti ipoglicemizzanti della Gymnema sono stati dimostrati in animali sottoposti a parziale

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control in type 2 diabetes mellitus. Quality of evidence: **MEDLINE and EMBASE were searched from January 1966 to August 2008 using the term type 2 diabetes in combination with each of the following terms for specific therapies selected by the authors: cinnamon, fenugreek, gymnema, green tea, fibre, momordica, chromium, and vanadium**. **Only human clinical trials were selected for review**. Main message: Chromium reduced glycosylated hemoglobin (HbA(1c)) and fasting blood glucose (FBG) levels in a large meta-analysis. **Gymnema sylvestre reduced HbA(1c) levels in 2 small open-label trials**. Cinnamon improved FBG but its effects on HbA(1c) are unknown. Bitter melon had no effect in 2 small trials. Fibre had no consistent effect on HbA(1c) or FBG in 12 small trials. Green tea reduced FBG levels in 1 of 3 small trials. Fenugreek reduced FBG in 1 of 3 small trials. Vanadium reduced FBG in small, uncontrolled trials. There were no trials evaluating microvascular or macrovascular complications or other clinical end points. Conclusion: **Chromium, and possibly gymnema, appears to improve glycemic control.** Fibre, green tea, and fenugreek have other benefits but there is little evidence that they substantially improve glycemic control. Further research on bitter melon and cinnamon is warranted. There is no complementary and alternative medicine research addressing microvascular or macrovascular clinical outcomes." *(Nahas R, Moher M. Complementary and alternative medicine for the treatment of type 2 diabetes. Can Fam Physician. 2009 Jun;55(6):591-6).*

[12] "Leaves of the Gymnema sylvestre (GS) plant have been used to treat diabetes mellitus for millennia, but the previously documented insulin secretagogue effects of GS extracts in vitro may be non-physiological through damage to the beta-cells. **We have now examined the effects of a novel GS extract (termed OSA) on insulin secretion from the MIN6 beta-cell line and isolated human islets of Langerhans**. **Insulin secretion from MIN6 cells was stimulated by OSA in a concentration-dependent manner**, with low concentrations (0.06-0.25 mg/ml) having no deleterious effects on MIN6 cell viability, while higher concentrations (> or = 0.5 mg/ml) caused increased Trypan blue uptake. **OSA increased beta-cell Ca2+ levels, an effect that was mediated by Ca2+ influx through voltage-operated calcium channels. OSA also reversibly stimulated insulin secretion from isolated human islets** and its insulin secretagogue effects in MIN6 cells and human islets were partially dependent on the presence of extracellular Ca2+. **These data indicate that low concentrations of the GS isolate OSA stimulate insulin secretion in vitro, at least in part as a consequence of Ca2+ influx, without compromising beta-cell viability.** Identification of the component of the OSA extract that stimulates regulated insulin exocytosis, and further investigation of its mode(s) of action, may provide promising lead targets for Type 2 diabetes therapy." *(Liu B, Asare-Anane H, Al-Romaiyan A, Huang G, Amiel SA, Jones PM, Persaud SJ. Characterisation of the insulinotropic activity of an aqueous extract of Gymnema sylvestre in mouse beta-cells and human islets of Langerhans. Cell Physiol Biochem. 2009;23(1-3):125-32).*

[13] "**To determine whether extracts of Gymnema sylvestre may have therapeutic potential for the treatment of non-insulin-dependent diabetes mellitus (NIDDM), we examined the effects of an alcoholic extract of G. sylvestre (GS4) on insulin secretion from rat islets of Langerhans and several pancreatic beta-cell lines**. GS4 stimulated insulin release from HIT-T15, MIN6 and RINm5F beta-cells and from islets in the absence of any other stimulus, and GS4-stimulated insulin secretion was inhibited in the presence of 1 mM EGTA. Blockade of voltage-operated Ca(2+) channels with 10 microM isradipine did not significantly affect GS4-induced secretion, and insulin release in response to GS4 was independent of incubation temperature. Examination of islet and beta-cell integrity after exposure to GS4, by trypan blue exclusion, indicated that concentrations of GS4 that stimulated insulin secretion also caused increased uptake of dye. Two gymnemic acid-enriched fractions of GS4, obtained by size exclusion and silica gel chromatography, also caused increases in insulin secretion concomitant with increased trypan blue uptake. **These results confirm the stimulatory effects of G. sylvestre on insulin release, but indicate that GS4 acts by increasing cell permeability, rather than by stimulating exocytosis by regulated pathways.** Thus the suitability of GS4 as a potential novel treatment for NIDDM can not be assessed by direct measurements of beta-cell function in vitro." *(Persaud SJ, Al-Majed H, Raman A, Jones PM. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J Endocrinol. 1999 Nov;163(2):207-12).*

pancreotomizzazione, mentre l'effetto non si manifestava in animali completamente pancreotomizzati. Studi effettuati con un estratto etanolico di Gymenma denominato GS-4 hanno poi rivelato un effetto di rigenerazione sulle cellule del Langherans in animali resi sperimentalmente diabetici, effetto associato alla riduzione del glucosio ematico[14]. Altri AA. avevano in precedenza trovato che in ratti resi sperimentalmente diabetici con berillio nitrato o streptozotocina l'estratto di *Gymnema sylvestre* raddoppiava il numero delle isole di Langerhans e di cellule beta secernenti insulina nel pancreas, riportando i livelli di glucosio nel sangue a valori normali[15]. Studi recenti, condotti anche con altre specie di Gymenma, dimostrano una spiccata azione protettiva sulle cellule beta pancreatiche nei confronti del danno ossidativo da parte del fitocomplesso della pianta[16].

L'azione antidiabetica della Gymnema sembra tuttavia dovuta alla combinazione di più meccanismi, tra cui un'interferenza con l'assorbimento intestinale di glucosio. E sono diversi gli AA. d'accordo nel ritenere che l'attività della *Gymnema sylvestre* non sia soltanto dovuta ad un'aumentata liberazione di insulina o ad una ridotta resistenza all'ormone, bensì anche ad un ridotto assorbimento del glucosio da parte dell'intestino[17]. Recenti studi, che confrontano l'azione ipoglicemizzante delle

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14 "**The structural alterations in pancreatic islets in streptozotocin-induced diabetic rats were studied after the administration of Gymnema sylvestre extract or its composition**. Diabetes mellitus was modeled by daily injection of streptozotocin (20 mg/kg for 5 days) and single injection of 0.2 ml of complete Freund's adjuvant, Only the animals with the blood glucose level exceeding 15 mmol/l were included in the experiment. B- and A-endocrinocytes were demonstrated using immunocytochemistry. The proportions of the area of the pancreatic islets, occupied by B- and A-endocrinocytes, as well as the volume fraction of the pancreatic islets within the pancreas, were determined. In the model of streptozotocin-induced diabetes, the part of the total islet area occupied by B-endocrinocytes, was diminished in the pancreatic islets located in all the zones of the gland. **Prophylactic administration of Gymnema sylvestre extract or its composition tended to restore the area occupied by B-endocrinocytes in the pancreatic islets. These results indicate the equal potency of the composition and extract of Gymnema sylvestre to induce the regeneration of B-endocrinocytes**." *(Snigur GL, Samokhina MP, Pisarev VB, Spasov AA, Bulanov AE. Structural alterations in pancreatic islets in streptozotocin-induced diabetic rats treated with of bioactive additive on the basis of Gymnema sylvestre. Morfologiia. 2008;133(1):60-4).*

15 *Prakash AO, Mathur S, Mathur R. Effect of feeding Gymnema sylvestre leaves on blood glucose in beryllium nitrate treated rats. J Ethnopharmacol. 1986 Nov;18(2):143-6.*

16 "The present study evaluated the molecular mechanism of antidiabetic property of Gymnema montanum leaf extract (GLEt) against alloxan-induced apoptotic cell death in rat insulinoma cells (RINm5F). The pre-treatment of GLEt (5 microg and 10 microg/ml) resulted in significant decrease in intracellular Ca(2+) concentration, nitric oxide (NO) production along with increase in mitochondrial membrane potential in alloxan (7mM/ml) treated cells. Further GLEt reduced apoptosis by inhibiting the release of cytochrome c and subsequent cleavage of PARP and caspase-3. The immunochemical staining of 8-hydroxydeoxyguanosine (8-OHdG) also evidenced the suppression of oxidative stress by GLEt. The cell cycle analysis, annexin-V labelling assay and TUNEL assay showed the suppression of apoptosis by the treatment of GLEt. Moreover, GLEt significantly increased the cellular antioxidant levels and decreased the lipid peroxides in alloxan-treated RINm5F cells. Taken together, **these findings suggest that G. montanum protects pancreatic beta-cells against reactive oxygen species (ROS) by counteracting with mitochondrial membrane permeability and inhibition of the apoptotic pathway.**" *(Ramkumar KM, Lee AS, Krishnamurthi K, Devi SS, Chakrabarti T, Kang KP, Lee S, Kim W, Park SK, Lee NH, Rajaguru P. Gymnema montanum H. protects against alloxan-induced oxidative stress and apoptosis in pancreatic beta-cells. Cell Physiol Biochem. 2009;24(5-6):429-40).*

17 "Extracts containing gymnemic acids, which were extracted from the leaves of Gymnema sylvestre (GS) as nine fractions, were evaluated for their effects on a high K(+)-induced contraction of guinea-pig ileal longitudinal muscles, on glucose transport mediated by the difference of glucose-evoked transmural potential difference (δPD) in the inverted intestine of guinea-pig and rat, and on blood glucose in rat… In conclusion, **it is suggested that some of the extracts containing gymnemic acids from GS leaves suppress the elevation of blood glucose level by inhibiting glucose uptake in the intestine**" *(Shimizu K, Iino A,*

diverse classi di sostanze contenute nel fitocomplesso della droga attraverso la verifica dell'attività di varie tipologie di estratti (estratto in acqua, etanolo, metanolo, esano e cloroformio) mostrano la massima attività per l'estratto etanolico della droga[18]. In particolare, le sostanze principalmente responsabili delle proprietà della Gymnema sull'equilibrio glicemico sembrano essere gli acidi gymnemici i quali - probabilmente con un meccanismo di inibizione competitiva a livello recettoriale che coinvolge il trasporto attivo del glucosio - intervengono sull'assorbimento degli zuccheri a livello intestinale, riducendolo[19]. Il blocco si instaura velocemente (circa 60 minuti) e permane per circa 5-6 ore, e grazie ad esso l'assorbimento degli zuccheri viene inibito per circa il 50%. Gli acidi gymnemici potrebbero anche agire inibendo le amilasi intestinali e pancreatiche e, quindi, riducendo la disponibilità del glucosio (con un meccanismo di azione simile all'acarbosio). Una inibizione dell'uptake e dell'utilizzazione del glucosio da parte di enterociti è stata osservata nella muscolatura liscia intestinale di cavia[20], e sembra confermata anche da una serie di ricerche sperimentali sulla

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Nakajima J, Tanaka K, Nakajyo S, Urakawa N, Atsuchi M, Wada T, Yamashita C. Suppression of glucose absorption by some fractions extracted from Gymnema sylvestre leaves. J Vet Med Sci 1997; 59: 245-51).

[18] "**In present study, we investigated hypoglycemic and antihyperglycemic potential of five extracts (water, ethanol, methanol, hexane, and chloroform) of four plants (i.e., seeds of Eugenia jambolana, fruits of Momordica charantia, leaves of Gymnema sylvestre, and seeds of Trigonella foenum graecum) alone and/or in combination with glimepiride in rats**. Ethanol extract of E. jambolana, water extract of M. charantia, **ethanol extract of G. sylvestre**, and water extract of T. graecum exhibited highest hypoglycemic and antihyperglycemic activity (most active) in rats among all the extracts, while hexane extracts exhibited least activities. Most active extracts were further studied to dose-dependent (200, 100, and 50 mg/kg body weight (bw)) hypoglycemic and antihyperglycemic effects alone and in combination with glimepiride (20, 10, and 5 mg/kg bw). The combination of most active extracts (200 mg/kg bw) and lower dose of glimepiride (5 mg/kg bw) showed safer and potent hypoglycemic as well as antihyperglycemic activities without creating severe hypoglycemia in normal rats, while higher doses (200 mg/kg bw of most active extracts, and 10 and 20 mg/kg bw of glimepiride) were generated lethal hypoglycemia in normal rats. **From this study, it may be concluded that the ethanol extract of E. jambolana seeds, water extract of M. charantia fruits, ethanol extract of G. sylvestre leaves, and water extract of T. graecum seeds have higher hypoglycemic and antihyperglycemic potential and may use as complementary medicine to treat the diabetic population** by significantly reducing dose of standard drugs." *(Yadav M, Lavania A, Tomar R, Prasad GB, Jain S, Yadav H. Complementary and Comparative Study on Hypoglycemic and Antihyperglycemic Activity of Various Extracts of Eugenia jambolana Seed, Momordica charantia Fruits, Gymnema sylvestre, and Trigonella foenum graecum Seeds in Rats. Appl Biochem Biotechnol. 2010 Apr;160(8):2388-400.*

[19] "The leaves of Gymnema inodorum (GI) have been known to be effective for some diseases including diabetes mellitus, rheumatic arthritis and gout. **The crude saponin mixtures extracted from GI leaves inhibited glucose absorption in the isolated intestinal tract and suppressed the increased blood glucose in rats**. In this study, **we examined the relationship between chemical structure and pharmacological activity of the four components from GI leave extracts** (GiA-1, GiA-2, GiA-5 and GiA-7). These components were the derivatives of (3beta,4alpha,16beta)-16,23,28-trihydroxyolean-12-en-3-yl-beta-D-glucopyranosiduroic acid. GiA-2, GiA-5 and GiA-7 that have suppressive effects on the high K+-induced contraction, an increase in deltaPD and the increased blood glucose level in the glucose tolerance test have -H at the 21st position and -CH2OH at 4beta of aglycon. On the other hand, GiA-1 that does not have any effects on the three parameters mentioned above has -H at the 21st position and -CH3 at 4beta of aglycon. In conclusion, **it is suggested that the inhibitory effect of triterpenoids in Gymnema leaves on glucose absorption from the intestinal tract relies on -CH2OH at 4beta**." *(Shimizu K, Ozeki M, Iino A, Nakajyo S, Urakawa N, Atsuchi M. Structure-activity relationships of triterpenoid derivatives extracted from Gymnema inodorum leaves on glucose absorption. Jpn J Pharmacol. 2001 Jun;86(2):223-9).*

[20] "Two substances… identified among the gymnemic acids are triterpene glycosides extracted from Gymnema sylvestre leaves. We examined the effects of GA1 or GA2 on high K(+)-induced contraction in the guinea-pig longitudinal muscle… **The inhibitory effect of GA1 and GA2 on smooth muscle were assumed to be a result of inhibiting glucose uptake, which is an energy source of the muscle**, whereas the inhibitory mechanisms were probably not mediated by Ca2+" *(Shimizu K, Abe*

liberazione di GIP (gastrointestinal polypeptide) a seguito di una infusione intraduodenale di glucosio: la contemporanea somministrazione di *Gymnema sylvestre* riduce la liberazione di GIP, ma lo stesso effetto non è ottenuto con il mannoeptulosio, un composto che blocca la glicolisi anaerobica[21]. Studi fatti nel ratto mostrano che l'estratto di *Gymnema sylvestre* riduce le contrazioni dell'intestino tenue indotte dal potassio, diminuisce il consumo di ossigeno nella parete intestinale e inibisce il potenziale transmurale dell'intestino tenue indotto dal glucosio, limitandone nettamente l'assorbimento. Somministrato alla dose di 1 g/kg nel ratto reso sperimentalmente diabetico con streptozotocina, l'estratto di *Gymnema sylvestre* ha ridotto la glicemia a digiuno e migliorato la tollerabilità al glucosio, senza modificare la liberazione di insulina dal pancreas[22]. I principi attivi della Gymnema[23] sembrerebbero quindi agire riducendo l'assorbimento intestinale di glucosio e forse sensibilizzando i recettori periferici dell'insulina ad un maggior trasporto intracellulare di glucosio, contribuendo così alla riduzione della glicemia.

In seguito ad uno studio effettuato direttamente sull'acido gymnemico IV, è stato visto che somministrato intraperitonealmente il principio attivo riduce i livelli di glucosio nei topi in cui era stato sperimentalmente indotto il diabete con streptozotocina con potenza comparabile alla glibenclamide, mentre non modifica i livelli di ematici di glucosio nei topi normali. L'acido gymnemico IV aumenta anche i livelli di insulina nel sangue[24]. Anche altri studi dimostrano gli effetti benefici degli

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T, Nakajyo S, Urakawa N, Atsuchi M, Yamashita C. Inhibitory effects of glucose utilization by gymnema acids in the guinea-pig ileal longitudinal muscle. J Smooth Muscle Res 1996; 32: 219-28).

21 "Gastric inhibitory peptide release into the portal vein in response to duodenal infusion of D-glucose was studied in the presence of a leaf extract of Gymnema sylvestre, purified gymnemic acid and inhibitors of some putative glucose sensors and carriers in the intestinal lumen… T**he results suggest that a glucose receptor, which interacts with the leaf extract of Gymnema sylvestre, purified gymnemic acid and phlorizin, exists for the release of immunoreactive gastric inhibitory peptide** and that the glucose receptor for gastric inhibitory peptide release is not likely to be identical with a glucose transporter or a vagal glucoreceptor in the lumen" *(Fushiki T, Kojima A, Imoto T, Inoue K, Sugimoto E. An extract of Gymnema sylvestre leaves and purified gymnemic acid inhibits glucose-stimulated gastric inhibitory peptide secretion in rats. J Nutr 1992; 122: 2367-73).*

22 "Effect of Gymnema sylvestre, R.Br. (G. sylvestre; GS4) on glucose homeostasis was studied in rats… **These results suggest the usefulness of G. sylvestre in the treatment of certain classes of non-insulin-dependent diabetes mellitus**" *(Okabayashi Y, Tani S, Fujisawa T, Koide M, Hasegawa H, Nakamura T, Fujii M, Otsuki M. Effect of Gymnema sylvestre, R.Br. on glucose homeostasis in rats. Diabetes Res Clin Pract 1990; 9: 143-8).*

23 *Liu HM, Kiuchi F, Tsuda Y. Isolation and structure elucidation of gymnemic acids, antisweet principles of Gymnema sylvestre. Chem Pharm Bull 1992;40: 1366-75.*

24 "We investigated the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanol extract of leaves of Gymnema sylvestre R. BR. (Asclepiadaceae) in streptozotocin (STZ)-diabetic mice. The saponin fraction (60mg/kg) reduced blood glucose levels 2 4h after the intraperitoneal administration. **Gymnemic acid IV, not the other 4 glycosides at doses of 3.4-13.4mg/kg reduced the blood glucose levels by 13.5-60.0% 6h after the administration comparable to the potency of glibenclamide, and did not change the blood glucose levels of normal mice. Gymnemic acid IV at 13.4 mg/kg increased plasma insulin levels in STZ-diabetic mice. Gymnemic acid IV (1 mg/mL) did not inhibit alpha-glycosidase activity in the brush border membrane vesicles of normal rat small intestines**. These results indicate that insulin-releasing action of gymnemic acid IV may contribute to the antihyperglycemic effect by the leaves of G. sylvestre. Gymnemic acid IV may be an anti-obese and antihyperglycemic pro-drug." *(Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I. Antihyperglycemic effects of gymnemic acid IV, a compound derived from Gymnema sylvestre leaves in streptozotocin-diabetic mice. J Asian Nat Prod Res. 2000;2(4):321-7).*

acidi gymenmici sul metabolismo glucidico[25]. Sono stati inoltre studiati gli effetti del conduritolo A, un'altra sostanza identificata nelle foglie di *Gymenma sylvestre*[26]. L'estratto standardizzato di *Gymnema sylvestre* è stato utilizzato con successo, alla posologia di 400 mg/die, nel trattamento di pazienti con NIDDM. 22 pazienti affetti da diabete di tipo 2 hanno assunto l'estratto GS4 per 18-20 mesi, in aggiunta alla loro terapia a base di ipoglicemizzanti orali. Al termine dello studio sono stati riscontrati una diminuzione significativa nel valore medio di glucosio e di HbA1c, insieme ad un progressivo incremento del rilascio pancreatico di insulina, il che potrebbe significare che la droga protegge le beta cellule del pancreas e ne favorisce la rigenerazione. Nel corso dello studio, i dosaggi dei farmaci sono stati ridotti, e ben cinque pazienti sono stati in grado di interrompere i medicinali completamente. Il miglioramento stabile del metabolismo del glucosio è stato dimostrato anche dalla notevole e significativa riduzione dell'emoglobina glicosilata, un parametro fedele ed indicativo di quanto efficace è stato nel tempo il controllo della glicemia[27].

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25 "**In a previous study, we found interaction of gymnemic acid (GA) with glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis. We now examined interaction of GA with glycolytic and related enzymes**. We found that (1) GA induced a band smearing of glycerol-3-phosphate dehydrogenase (G3PDH) as well as that of GAPDH in SDS-PAGE, (2) GA diminished the G3PDH band detected by an antibody to phosphoserine, and (3) GA inhibited the G3PDH activity. The GA-induced smearing of the G3PDH band was diminished by prior incubation of GA with gamma-cyclodextrin. GA gave no effects on the electrophoretic and phosphoserine bands of other glycolytic enzymes. NAD and NADH diminished the GA-induced smearing of the G3PDH and GAPDH bands in different concentration-dependent manner. Pretreatment of G3PDH with heated SDS-containing buffer or pretreatment with hydroxylamine diminished the GA-induced smearing of G3PDH. Deacylation of GA by alkaline hydrolysis diminished the smearing of G3PDH band, thereby indicating that the acyl moieties of GA were necessary for the GA-induced smearing of G3PDH. These results indicated the **interaction of GA with G3PDH, an enzyme involved in glycerol metabolism**. **These studies suggest that GA may have some pharmacological activities including antidiabetic activity and lipid lowering effects via interaction with GAPDH and G3PDH**." *(Ishijima S, Takashima T, Ikemura T, Izutani Y. Gymnemic acid interacts with mammalian glycerol-3-phosphate dehydrogenase. Mol Cell Biochem. 2008 Mar;310(1-2):203-8).*

26 "**To investigates the mechanism of hypooglycemic effect of conduritol A of stems of Gymnema sylvestre**, fourteen days later after administration, observation is taken on the change of these mice and rats weight, the FBG, TG, CHO, SOD, MDA, INS, TNF in serum were also detected with enzymology method and Radioimmuoassay method. Take the liver to determine the disposal of glucose. Take the pancreas to do the HE and immunohistochemistrial staining, and show pancreas islet beta-cell. Calulate thymus, pancreas, splenica index. Result: Compared with diabetic model mice, high and middosage of conduritol A could remarkably reduce fasted blood sugar in diabetic rats induced by alloxan ($P < 0.01$). Significantly increase the level of serum insulin ($P < 0.05$). Activity of SOD was obviously increased, and amount of MDA was obviously decreased ($P < 0.05$). The amount of conduritol A disposal of glucose was obviously increased ($P < 0.05$). Significantly increase thymus, pancreas, splencia index ($P < 0.01$ or 0.05); inhibited the atrophy of thymus, pancreas, splencias of the diabetic rats induced by alloxan. Compared with diabetic model group, cell structure and form of conduritol A had been some way improved. The immunohistochemistry results showed that **beta-cells numbers of pancreas in each conduritol A group were more than those in the model group**. Conclusion: **Conduritol A could have an effect on regulating the metabolism of blood lipid, free-radical scavenging, enhancing the antioxidant ability, potentiating immune function. Promoting synthesis of hepatic to decrease fasted blood suger.**" *(Wei JH, Zhen HS, Qiu Q, Chen J, Zhou F. Experimental [corrected] study of hypoglycemic activity of conduritol A of stems of Gymnema sylvestre. Zhongguo Zhong Yao Za Zhi. 2008 Dec;33(24):2961-5).*

27 "The effectiveness of GS4, an extract from the leaves of Gymnema sylvestre, in controlling hyperglycaemia was investigated in 22 Type 2 diabetic patients on conventional oral anti-hyperglycaemic agents. GS4 (400 mg/day) was administered for 18-20 months as a supplement to the conventional oral drugs. During GS4 supplementation, the patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, and conventional drug dosage could be decreased. Five of the 22 diabetic patients were able to discontinue their conventional drug and maintain their blood glucose homeostasis with GS4 alone. **These data suggest that the β cells may be regenerated/repaired in Type 2 diabetic patients on GS4 supplementation. This is supported by the appearance of raised insulin levels in the serum of patients after**

Un discreto successo terapeutico è stato ottenuto, sempre alla posologia di 400 mg/die di estratto, anche nel trattamento del diabete di tipo 1 (giovanile o insulino-dipendente). L'estratto standardizzato di Gymnema GS4 è stato somministrato a 27 pazienti affetti da diabete mellito di tipo 1 alla dose di 400 mg/giorno per un periodo di 10-12 mesi. Un gruppo di controllo, costituito da 37 pazienti, ha continuato la terapia con solo insulina. Nel gruppo trattato con Gymnema le richieste di insulina sono diminuite della metà, anche l'emoglobina glicosilata è calata in modo significativo e la diminuzione della concentrazione di glucosio nel sangue è stata in media da 232 mg/dl a 152 mg/dl, mentre il gruppo controllo non ha subito variazioni significative dei livelli di glucosio o delle richieste di insulina[28]. A questo proposito merita di essere segnalata l'osservazione che, in ratti trattati con streptozotocina (una sostanza tossica per le β-cellule pancreatiche che inibisce irreversibilmente la produzione e la liberazione di insulina), la somministrazione di *Gymnema sylvestre* per un periodo di 20-60 giorni ha determinato un aumento delle concentrazioni plasmatiche di insulina – cadute a valori vicini allo zero dopo il trattamento con streptozotocina. Questo dato – che merita ulteriori conferme sperimentali – ha indotto gli AA. ad ipotizzare un effetto rigenerante della Gymnema sulle isole di Langherans[29]. Nel corso di uno studio mirato a valutare gli effetti della Gymnema sull'ipertensione collegata a condizioni di iperinsulinemia o insulino-resistenza, si è visto che la *G. sylvestre* ha provocato un significativo abbassamento del colesterolo, suggerendo un qualche effetto della droga sul metabolismo. Il fitocomplesso non ha tuttavia mostrato effetti sui valori pressori, indicando che la droga avrebbe proprio l'effetto di stimolare il rilascio di insulina rigenerando le cellule beta pancreatiche, ma non quello di aumentare la sensibilità periferica all'insulina. Solo le sostanze in grado di abbassare i livelli di insulina circolante (meccanismo ipotizzato, p.e., per il cromo), possono infatti essere utili nel trattamento della pressione sanguigna elevata collegata a condizioni di iperinsulinemia o insulino-resistenza[30].

GS4 supplementation." *(Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, Shanmugasundaram ER. Antidiabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. J Ethnopharmacol 1990; 30: 295-300).*

[28] "GS4, a water-soluble extract of the leaves of Gymnema sylvestre, was administered (400 mg/day) to 27 patients with insulin-dependent diabetes mellitus (IDDM) on insulin therapy. Insulin requirements came down together with fasting blood glucose and glycosylated haemoglobin (HbA1c) and glycosylated plasma protein levels. While serum lipids returned to near normal levels with GS4 therapy, glycosylated haemoglobin and glycosylated plasma protein levels remained higher than controls. IDDM patients on insulin therapy only showed no significant reduction in serum lipids, HbA1c or glycosylated plasma proteins when followed up after 10-12 months. **GS4 therapy appears to enhance endogenous insulin, possibly by regeneration/ revitalisation of the residual β cells in insulin-dependent diabetes mellitus."** *(Shanmugasundaram ER, Rajeswari G, Baskaran K, Rajesh Kumar BR, Radha Shanmugasundaram K, Kizar Ahmath B. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol 1990; 30: 281-94).*

[29] "Two water soluble extracts, GS3 and GS4, obtained from the leaves of Gymnema sylvestre, were tested in streptozotocin treated rats for their effects on blood glucose homeostasis and pancreatic endocrine tissue… **This herbal therapy appears to bring about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas.**" *(Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. J Ethnopharmacol 1990; 30: 265-79).*

[30] "Effects on systolic blood pressure (SBP) of ingesting three agents reported to influence insulin metabolism, i.e., chromium polynicotinate, bis(maltolato)oxovanadium (BMOV), and the herb, Gymnema sylvestre, were assessed simultaneously in

Sovrappeso e obesità. Riducendo l'assorbimento intestinale di glucosio, la G*ymnema sylvestre* trova indicazione anche nel trattamento coadiuvante del sovrappeso e dell'obesità, due condizioni peraltro spesso presenti in concomitanza ad un diabete mellito. É stato poi osservato per la droga un modesto effetto di riduzione dei livelli dei trigliceridi, del colesterolo totale, delle VLDL e delle LDL. L'effetto della *Gymnema sylvestre* è particolarmente evidente nei soggetti con una dieta ipercalorica, sbilanciata a favore dei carboidrati (pane, pasta, dolci, ecc); in queste situazioni, la pianta, preferibilmente in associazione con altri fitocomplessi, può essere vantaggiosamente inserita in un programma di riduzione del peso corporeo[31].

Attività sulle papille gustative. Una attività molto interessante descritta in letteratura è la capacità di alcuni composti contenuti nella *Gymnema sylvestre*, di modificare la funzionalità delle papille gustative e di inibire il gusto per il dolce[32]. L'attività è presente solo se il fitocomplesso viene masticato e tenuto a contatto con la lingua per alcuni secondi, mentre non si manifesta se il fitocomplesso è assunto e deglutito in forma di capsule o compresse. L'attività è stata riferita sia ad una serie di triterpeni isolati dalle foglie *Gymnema sylvestre* e da altri fitocomplessi[33], sia ad un polipeptide – la gurmarina – la cui sequenza aminoacidica è stata dettagliatamente identificata,

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spontaneously hypertensive rats (SHR). (…) Chromium decreases the portion of SBP) elevated by high sucrose intake as shown previously, but high levels of sucrose ingestion can eventually overcome this. BMOV overcame sucrose-induced elevation of SBP as well as some of the "genetic hypertension." Different from chromium, this decrease was not overcome by high levels of dietary sucrose. **The significant lowering of cholesterol with G. sylvestre ingestion indicates some effect on metabolism**, but G. sylvestre did not lower and even raised SBP." *(Preuss HG, et al. Comparative Effects of Chromium, Vanadium and Gymnema sylvestre on Sugar-Induced Blood Pressure Elevations in SHR. J Am Coll Nutr.1998 Apr;17(2):116-23).*

31 "The efficacy of optimal doses of highly bioavailable (-)-hydroxycitric acid (HCA-SX) alone and in combination with niacin-bound chromium (NBC) and a standardized Gymnema sylvestre extract (GSE) on weight loss in moderately obese subjects was evaluated by monitoring changes in body weight, body mass index (BMI), appetite, lipid profiles, serum leptin and excretion of urinary fat metabolites…" *(Preuss HG, Bagchi D, Bagchi M, Rao CV, Dey DK, Satyanarayana S. Effects of a natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX plus niacin-bound chromium and Gymnema sylvestre extract on weight loss. Diabetes Obes Metab. 2004 May;6(3):171-80).*

32 "Electrophysiological and behavioral experiments were performed to reveal taste properties of "umami" substances such as monosodium glutamate (MSG) and disodium inosine monophosphate (IMP) in rats… **A new sweet taste inhibitor (Gymnema sylvestre extract) strongly suppressed neural responses to mixtures of MSG and IMP as well as sucrose, but only weakly or negligibly to individual solutions of these umami substances**…" *(Yamamoto T, Matsuo R, Fujimoto Y, Fukunaga I, Miyasaka A, Imoto T. Electrophysiological and behavioral studies on the taste of umami substances in the rat. Physiol Behav 1991; 49: 919-25).*

33 *Suttisri R, Lee IS Kinghorn AD. Plant-derived triterpenoid sweetness inhibitors. J Ethnopharmacol., 47(1):9-26, 1995.*

insieme alla sua struttura tridimensionale[34,35].

La gurmarina altera temporaneamente la percezione del sapore dolce a livello delle papille gustative, senza modificare quella del salato, dell'acido e dell'amaro; in particolare, in seguito all'azione della gurmarina viene ridotta del 40-50% la capacità di percepire il gusto dolce dei seguenti composti: saccarosio, fruttosio, lattosio e maltosio[36]. L'attività elettrofisiologica della gurmarina è stata studiata *in vitro* nel topo[37] e *in vivo* sulle papille gustative di ratto. Alla concentrazione di 0.5 µM ed a pH 4.5 (punto isoelettrico del polipeptide), la gurmarina blocca la risposta elettrica delle papille gustative allo zucchero, agli aminoacidi dolci ed alla saccarina. L'effetto è massimale alla concentrazione di 5 µM in seguito all'applicazione diretta sulla lingua, mentre è assente dopo somministrazione endovenosa, indicando che l'effetto della gurmarina è diretto alla porzione apicale delle papille gustative[38].

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34 "**Gurmarin is a 35-residue polypeptide from the Asclepiad vine Gymnema sylvestre. It has been utilised as a pharmacological tool in the study of sweet-taste transduction because of its ability to selectively inhibit the neural response to sweet tastants in rats**. We have chemically synthesised and folded gurmarin and determined its threedimensional solution structure to high resolution using two-dimensional NMR spectroscopy. Structure calculations utilised 612 interproton-distance, 19 dihedral-angle, and 18 hydrogen-bond restraints. The structure is well defined for residues 3±34, with backbone and heavy atom rms differences of 0.27 ^ 0.09 A Ê and 0.73 ^ 0.09 A Ê , respectively. Gurmarin adopts a compact structure containing an antiparallel b-hairpin (residues 22±34), several well-defined b-turns, and a cystine-knot motif commonly observed in toxic and inhibitory polypeptides. Despite striking structural homology with d-atracotoxin, a spider neurotoxin known to slow the inactivation of voltage-gated Na+ channels, we show that gurmarin has no effect on a variety of voltage-sensitive channels." *(Fletcher JI, Dingley AJ, Smith R, Connor M, Christie MacDonald J, King GF. High-resolution solution structure of gurmarin, a sweet-taste-suppressing plant polypeptide. Eur. J. Biochem. 1999; (264):525-533).*

35 *Arai K, Ishima R, Morikawa S, Miyasaka A, Imoto T, Yoshimura S, Aimoto S, Akasaka K. Three-dimensional structure of gurmarin, a sweet taste-suppressing polypeptide. J Biomol NMR 1995; 5: 297-305.*

36 "**Gurmarin (10 microg/ml), a protein extracted from Gymnema sylvestre, depressed significantly (40-50%) the phasic taste responses to sugars (sucrose, fructose, lactose, and maltose) and saccharin sodium recorded from the greater superficial petrosal nerve (GSP) innervating palatal taste buds in the rat. However, no significant effect of gurmarin was observed for taste responses to NaCl, HCl, and quinine hydrochloride**. Phasic responses to D-amino acids that taste sweet to humans (His, Asn, Phe, Gln) were also depressed, but gurmarin treatment was without significant effect on taste responses to D-Trp and D-Ala, six L-amino acids (His, Asn, Phe, Gln, Trp, and Ala), and two basic amino acid HCl salts (Arg and Lys). With the exception of D-Trp, these inhibitory effects of gurmarin on GSP taste responses were related to the rat's preference for these substances." *(Harada S, Kasahara Y. Inhibitory effect of gurmarin on palatal taste responses to amino acids in the rat. Am J Physiol Regul Integr Comp Physiol. 2000 Jun;278(6):R1513-7).*

37 "The inhibitory effects of gurmarin (a peptide isolated from the leaves of Gymnema sylvestre) on sweet taste responses were studied by examining the chorda tympani nerve responses to various taste substances before and after lingual treatment with gurmarin in C57BL and BALB mice… **These results strongly suggest that there are at least two types of sweet taste receptors in mice, gurmarin-sensitive and -insensitive**. Probably, C57BL and BALB mice share an identical gurmarin-insensitive receptor, and C57BL mice also have agurmarin-sensitive receptor." *(Ninomiya Y; Imoto T. Gurmarin inhibition of sweet taste responses in mice. Am J Physiol 1995; 268: R1019-25).*

38 "The effect of an anti-sweet peptide, gurmarin purified from the leaves of Gymnema sylvestre, was studied electrophysiologically on taste responses of the rat chorda tympani… **These results suggest that gurmarin acts on the apical side of the taste cell, possibly by binding to the sweet taste receptor protein.**" *(Miyasaka A, Imoto T. Electrophysiological characterization of the inhibitory effect of a novel peptide gurmarin on the sweet taste response in rats. Brain Res 1995; 676: 63-8).*

Altre attività. L'estratto etanolico delle foglie di *Gymnema sylvestre* ha mostrato una buona attività antibatterica nei confronti di *Bacillus pumilis*, *Bacillus subtilis*, *Pseudomonas aeruginosa* e *Staphylococcus aureus*, mentre è risultato inattivo verso *Proteus vulgaris* ed *Escherichia coli*[39].

Tollerabilità. Sulla sicurezza degli estratti di *Gymenma Sylvestre,* soprattutto riferita all'utilizzo per lunghi periodi, abbiamo ancora pochi elementi, anche se la pianta non è mai stata associata con segnalazioni di tossicità nell'uomo. Per il suo comprovato effetto ipoglicemizzante è tuttavia possibile un'interazione con altri farmaci ipoglicemizzanti, in modo particolare ipoglicemizzanti orali per la terapia del diabete mellito. É stato infatti visto che un estratto di Gymnema (GS-4) ha aumentato gli effetti di ipoglicemizzanti di farmaci come glibenclamide e tolbutamide (J Ethnopharmacol 1990).

[39] "**The ethanolic extract of Gymnema sylvestre leaves demonstrated antimicrobial activity against Bacillus pumilis, B. subtilis, Pseudomonas aeruginosa and Staphylococcus aureus** and inactivity against Proteus vulgaris and Escherichia coli." *(Satdive RK, Abhilash P, Fulzele DP. Antimicrobial activity of Gymnema sylvestre leaf extract. Fitoterapia. 2003 Dec;74(7-8):699-701).*