Ginseng

Panax ginseng

Nome botanico

Panax ginseng C. A. Mey. *(Araliaceae)*

Parti usate

Radici.

Componenti principali

Terpeni tra cui ginsenosidi o panaxosidi (prevalentemente Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2 e Rh1). Peptidoglicani (panaxani A-E e Q-U).

Attività farmacologica

Attività adattogena. Azione stimolante le funzioni cognitive e le performance fisiche; attività tonica e corroborante generale.

Impiego clinico

Intensa attività fisica e/o mentale. Stati di sovraffaticamento e di esaurimento psicofisico; astenia, convalescenze di malattie debilitanti; situazioni di stress e di depressione reattiva.

Controindicazioni

Nessuna controindicazione nota.

Avvertenze e speciali precauzioni d'uso

Il Ginseng produce effetti di stimolazione centrale; si consiglia pertanto di assumere il prodotto al mattino e/o nel primo pomeriggio. 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 medico. Se ne sconsiglia l'uso nei soggetti ipertesi.

Interazioni

L'assunzione di Ginseng è stata correlata con una blanda riduzione dei livelli di glucosio nel sangue. Inoltre è stato riportato un caso di possibile interazione del ginseng con farmaci anticoagulanti a base di warfarina, tuttavia il meccanismo resta sconosciuto e sono necessari studi più approfonditi.

Effetti indesiderati

Dalle informazioni trovate nelle monografie ufficiali del Ginseng si evince che gli effetti collaterali sono alquanto rari e le conclusioni riportate sono che l'uso del Ginseng non è associato a gravi effetti avversi se assunto ai dosaggi raccomandati.

Note Bibliografiche

Composizione

I principali componenti del Ginseng sono i ginsenosidi, un gruppo di saponine triterpeniche variamente sostituite. Le varie specie di Ginseng (*Panax, Quinquefolium, Notoginseg, Japonicus*, *Trifolius*) possono essere distinte in base ai ginsenosidi prevalenti nella droga: in particolare i ginsenosidi prevalenti nella specie *Panax* (Ginseng cinese o coreano), senza dubbio la specie più diffusamente utilizzata, sono Rb1, Rb2, Rc, Re, Rg1; mentre ad esempio nel Ginseng americano (*Quinquefolium*) prevalgono i ginsenosidi Rb1 e Re. La composizione del *Panax ginseng* in funzione della specie e delle condizioni di coltivazione è stata oggetto di una recente rassegna, insieme con le principali attività farmacologiche dei 28 ginsenosidi identificati fino ad ora[1]. Le sostanze isolate dalla radice di *Panax ginseng*, riportate in letteratura dal 1989 ad oggi, sono i ginsenosidi del gruppo dell'oleanolico: Ro; ed i ginsenosidi del gruppo del dammarano: Ra, Rb1, Rb2, Rb3, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rh1 ed Rh2. I ginsenosidi del gruppo del dammarano vengono a loro volta suddivisi, in base alla struttura, in derivati del protopanaxadiolo (Rb1, Rb2, Rb3, Rc e Rd) e derivati del protopanaxatriolo (Re, Rf, Rg1, Rg2 e Rh1). Tra gli altri composti presenti abbiamo poi un gruppo di polisaccaridi complessi, i panaxani A-E e Q-U; panaxinolo; polipeptidi; vitamine, soprattutto del gruppo B; sali minerali e oligoelementi; tracce di olio essenziale.

Farmacocinetica

I metaboliti dei ginsenosidi sono stati scarsamente studiati in relazione alle proprietà farmacocinetiche, in quanto esistono più di 10 ginsenosidi, ognuno dei quali forma almeno 5 diversi metaboliti. Tuttavia in studi sperimentali *in vivo* è stato riscontrato che a seguito di somministrazioni orali di ginsenosidi Rg1, Rb2, Rd ed Re purificati o semipurificati, i risultati mostrano che il ginsenoside Rb2 ha avuto un'emivita di eliminazione più lunga (445 minuti) e una clearance metabolica e renale inferiore rispetto ai ginsenosidi Rg1 e Re, naturalmente a causa di una più alta capacità di binding alle proteine plasmatiche. Nessun ginsenoside è stato riscontrato nei campioni di plasma o urine dopo la somministrazione orale; anche l'analisi per il ginsenoside Rg1 dei campioni fecali ha dato risultato negativo[2]. La farmacocinetica del ginsenoside Rg1, dopo una somministrazione

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1 *Liu CX, Xiao PG. Recent advances on ginseng research in China. J Ethnopharmacol 1992; 36: 27-38.*

2 "The pharmacokinetics of ginsenosides A1, A2, B2, and C were studied in rabbits and were best described with a one-component open model. Ginsenoside C (protopanaxadiol group ginseng saponin) showed a significantly longer half-life, higher plasma protein binding, and lower metabolic and renal clearance than ginsenosides A1, A2, and B2 (protopanaxatriol group ginseng saponins). All ginsenosides except ginsenoside A1 were slowly absorbed after intraperitoneal administration. Ginsenosides were not found in rabbit plasma or urine samples after oral administration. The observed differences in the pharmacokinetics of the ginsenosides may be ascribed to differences in protein binding. Ginsenoside C was more toxic than ginsenoside A2 after intraperitoneal administration to mice. Toxicity was not observed after oral administration of any of the ginsenosides." (*Chen SE, Sawchuk RJ, Staba EJ. American ginseng. III. Pharmacokinetics of ginsenosides in the rabbit. Eur J Drug*

orale ha mostrato un assorbimento rapido dell'1,9-20% di Rg1 con una t_{max} di 30 minuti[3]. L'Rb1 somministrato per via orale è stato scarsamente assorbito (circa lo 0,1%) dall'intestino del ratto. Mentre l'escrezione di Rb1 dopo somministrazione endovenosa è stata bifasica, con un tempo di dimezzamento di 11,6 minuti per la fase α e di 14,6 ore per la fase β. L'escrezione è avvenuta prevalentemente nelle urine (44% entro 120 ore) e scarsamente nella bile (0,8% entro 24 ore)[4]. In 4 volontari sani dopo l'ingestione orale di preparati di polvere di Ginseng e di estratto di Ginseng, corrispondenti a 6,2-27,6 mg/die di ginsenosidi è stata riscontrata l'escrezione urinaria, dose-dipendente, di glicosidi del 20(S)-protopanaxatriolo (1,5% della dose)[5]. Grazie all'ausilio di analisi gascromatografiche associate alla spettrometria di massa GC-MS con monitoraggio selettivo di ioni, sono stati quantificati nelle urine di atleti che affermavano di aver consumato preparati di ginseng da almeno 10 giorni prima della raccolta delle urine gli agliconi dei ginsenosidi alla concentrazione di 2-35 ng/ml[6].

Farmacologia e meccanismo di azione

I ginsenosidi – principali componenti della radice di Ginseng – sono caratterizzati da meccanismi d'azione differenti, e di conseguenza da differenti attività farmacologiche. In relazione alla prevalenza dei vari ginsenosidi nelle varie specie si osservano quindi azioni farmacologiche leggermente diverse. I meccanismi di azione descritti per alcuni dei principali ginsenosidi del *Panax ginseng* sono:

Metab Pharmacokinet 1980;5:161-8..)

[3] *Odani T, Tanizawa H, Takino Y. Studies on the absorption, distribution, excretion and metabolism of ginseng saponins. II. The absorption, distribution and excretion of ginsenoside Rg1 in the rat. Chem Pharm Bull 1983;31:292-8.*

[4] *Odani T, Tanizawa H, Takino Y. Studies on the absorption, distribution, excretion and metabolism of ginseng saponins. III. The absorption, distribution and excretion of ginsenoside Rb1 in the rat. Chem Pharm Bull 1983;31:1059-66..*

[5] "Rb1 was hydrolyzed to 20(R,S)-ginsenoside Rg3 in 0.1 N HCl. On the other hand, hydroperoxidation of Rb1 occurred in rat stomach; the major hydroperoxide was separated and identified as the 25-hydroperoxy-23-ene derivative of Rb1 (VIII) by 1H- and 13C-nuclear magnetic resonance and fast atom bombardment mass spectrometry. The decomposition modes of 20(S)-ppd saponins (Rb1 and Rb2) differed from that of 20(S)-protopanaxatriol saponin (Rg1) in rat stomach. In rat large intestine, five decomposition products of Rb1 were observed by thin-layer chromatography, and these were identified as gypenoside XVII (G-XVII), ginsenoside Rd (Rd), ginsenoside F2 (F2), compound K (C-K) and VIII. The decomposition modes of Rb1 and Rb2, both 20(S)-ppd saponins, are considered to be different because of the hydrolysis rate in the terminal sugar moiety at the C-20 hydroxyl group in the rat large intestine." *(Karikura M, Miyase T, Tanizawa H, Taniyama T, Takino Y. Studies on absorption, distribution, excretion and metabolism of ginseng saponins. VII. Comparison of the decomposition modes of ginsenoside-Rb1 and -Rb2 in the digestive tract of rats. Chem Pharm Bull 1991;39:2357-61).*

[6] "hydrolysis, epimerization and hydration in the side-chain of the aglycone moiety of ginsenosides may occur in the liquid formulations under weak acidic conditions (pH 3.0-3.5 with 9-10% of alcohol at room temperature). The new method was also used to determine the aglycones of ginsenosides in urine samples from Swedish athletes stating that they had consumed ginseng preparations within 10 days before urine collection. Out of the 65 samples analysed, 60 were found to contain 20(S)-protopanaxatriol. The concentrations of 20(S)-protopanaxatriol ginsenosides varied from 2 to 35 ng ml-1 urine " *(Cui JF, Garle M, Björkhem I, Eneroth P. Determination of aglycones of ginsenosides in ginseng preparations sold in Sweden and in urine samples from Swedish athletes consuming ginseng. Scand J Clin Lab Invest 1996;56:151-60)*

Attività calcio antagonista sui canali lenti del calcio[7,8] dimostrata da una riduzione dell'ampiezza del potenziale di azione osservato in miocardiociti[9] e mediata da un legame a proteine GTP-dipendenti[10.] In letteratura vengono riportati anche dati su l'induzione dei canali del calcio e potassio da parte dei ginsenosidi[11], in particolare il ginsenoside Rg3[12], che comportano una vaso rilassamento in un modello ex vivo.

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[7] "To identify the calcium channel blockade and anti-free-radical actions of panaxadiol saponins Rb1, Rb2, Rb3, Rc, and Rd… **Rb1, Rb2, Rb3, and Rc had both the calcium channel blockade and anti-free-radical actions."** *(Zhong GG, Sun CW, Li YY, Qi H, Zhao CY, Jiang Y, Wang XM, Yang SJ, Li H. Calcium channel blockade and anti-free-radical actions of panaxadiol saponins Rb1, Rb2, Rb3, Rc, and Rd. Chung Kuo Yao Li Hsueh Pao 1995; 16:255-60).*

[8] Wistar rat ventricular myocytes were isolated. Panaxadiol saponins 1500 μg.ml-1, panaxatriol saponins 300 μg.ml-1, verapamil 37.5 μg.ml-1, or BAY k 8644 5 μmol.L-1 were added into the bath solution separately. The single channel activities of L, T, and B type calcium channels were recorded before and after the administration, using voltage patch-clamp technique in cell-attached configuration. The **calcium channel blockade effect of these 2 groups of ginsenosides was authenticated verified. The mechanism existed in the decrease in both the open time and the open-state probability of the calcium channe**l." *(Zhang WJ; Zhong GG; Jiang Y; Wang XM; Wang ZF. Single channel analysis on calcium channel blockade action of panaxadiol and panaxatriol saponins on cultured rat ventricular myocytes. Chung Kuo Yao Li Hsueh Pao. 1994 Mar. 15(2). P 173-6).*

[9] "Wistar rat myocardial cells were cultured. **PDS 20-80 μg.ml-1; PTS 1.25-20 μg.ml-1 dose-dependently decreased their action potential parameters, indicating the possibility of being concerned in the blockage of Ca channel**". *(Zhong GG, Jiang Y, Wang XQ, Yue G. Department of Physiology, Norman Bethune University of Medical Sciences, Changchun, China. Effects of panaxadiol and panaxatriol saponins on action potentials of normal and xanthine-xanthine oxidase damaged cultured myocardial cells. Chung Kuo Yao Li Hsueh Pao 1991; 12: 256-60).*

[10] "The effect of Panax ginseng root extract on Ca2+ current of adult rat trigeminal ganglion neurons was investigated using whole-cell patch-clamp methods. The application of P. ginseng root extract (100 μg/ml) produced rapid, reversible reduction of the Ca2+ current by 22 ± 4%. **Treatment with pertussis toxin (250ng/ml) for 16 h reduced the inhibition to 4 ± 1%**… Thus, P. ginseng root extract acts on sensory neurons through a similar pathway as mu-type opioids: both inhibit Ca2+ channels through pertussis toxin-sensitive GTP-binding proteins. However, the receptor for P. ginseng root extract is not an α 2-adrenergic, GABAB, muscarinic, or opioid receptor". *(Nah SY; McCleskey EW. Department of Cell Biology and Physiology #8228, Washington University School of Medicine, St. Louis, MO 63110. Ginseng root extract inhibits calcium channels in rat sensory neurons through a similar path, but different receptor, as mu-type opioids. J Ethnopharmacol. 1994 Mar. 42(1). P 45-51).*

[11] "Ginsenosides (GS), an extract of Panax ginseng, in particular GS induced vasorelaxation also involves Ca2+ -activated K+ (KCa) channels in vascular smooth muscle cells (VSMC) in addition to endothelium-derived NO. GS induced vasorelaxation in rat aortic rings, which had been precontracted with phenylephrine, in a concentration-dependent manner. This GS-induced relaxation was partially reversed by tetraethylammonium (TEA), an inhibitor of KCa channels; methylene blue (MB), an inhibitor of soluble guanylate cyclase; as well as Nomega-nitro-L-arginine (L-NNA), but not by glybenclamide. In cultured VSMC and endothelial cells, KCa channels were activated by GS. This action was abolished by TEA, but was not blocked by glybenclamide. In addition, the GS-induced activity of KCa channels was partially inhibited by MB or H-8. These results indicate that the activation of KCa channels involved, at least in part, the GS-induced vasorelaxation of rat aorta." *(Li Z, Chen X, Niwa Y, Sakamoto S, Nakaya Y.Involvement of Ca2+ -activated K+ channels in ginsenosides-induced aortic relaxation in rats. J Cardiovasc Pharmacol. 2001 Jan;37(1):41-7.)*

[12] " The purpose of the present study was to characterize the mechanism underlying the direct relaxing activity of ginsenosides on vascular smooth muscle. The total ginsenoside mixture, ginsenosides from either the protopanaxadiol group or the protopanaxatriol group, and the ginsenoside Rg3 from the protopanaxatriol group caused a concentration-dependent relaxation of rat aortic rings without endothelium contracted with 25 x 10(-3) M KCl but affected only minimally those contracted with 60 x 10(-3) M KCl. Ginsenoside Rg3 was the most potent relaxing agonist. Relaxations elicited by ginsenoside Rg3 were markedly reduced by tetraethylammonium, a blocker of non-selective K+ channels, but not by glibenclamide, a blocker of ATP-sensitive K+ channels. Ginsenoside Rg3 significantly inhibited Ca2+-induced concentration-contraction curves and the 45Ca2+ influx in aortic rings incubated with 25 x 10(-3) M KCl whereas these responses were not affected in rings incubated with 60 x 10(-3) M KCl. Ginsenoside Rg3 caused a time- and concentration-dependent efflux of 86Rb from aortic rings that was inhibited by tetraethylammonium but not by glibenclamide. These findings indicate that ginsenoside Rg3 is a potent inhibitor of vascular smooth muscle tone and that this effect seems to be due to an inhibition of Ca2+ influx and stimulation of K+ efflux, possibly

Inibizione delle fosfodiesterasi calmodulina-dipendenti[13]; stimolazione della produzione di nitrossido[14]; inibizione della sintesi del trombossano[15].

Effetti sulle pompe di membrana. Alcuni AA. hanno riportato una inibizione della Na^+/K^+ ATPasi di membrana da parte del ginsenoside Rb1[16]; altri AA. un'attivazione dell'ATPasi nel sinaptosoma cerebrale[17]..

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e i più noti impieghi clinici descritti per il fitocomplesso di *Panax ginseng* sono:

Attività adattogena. Aumento del rendimento fisico e mentale. Il *Panax ginseng* viene utilizzato da secoli dalla medicina popolare cinese come tonico, stimolante e corroborante e per migliorare il senso generale di benessere fisico e psicologico[18]. Applicazioni che trovano conferma anche nella medicina occidentale[19]: utilizzato come tonico, energetico e stimolante delle funzioni cognitive e mnemoniche, utile in caso di intensa attività mentale e/o fisica e negli stati di astenia ed esaurimento psicofisico; viene inoltre efficacemente impiegato dagli atleti come ergogenico nelle prestazioni

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via activation of tetraethylammonium-sensitive K+ channels." *(Kim ND, Kang SY, Kim MJ, Park JH, Schini-Kerth VBThe ginsenoside Rg3 evokes endothelium-independent relaxation in rat aortic rings: role of K+ channels. Eur J Pharmacol. 1999 Feb 12;367(1):51-7.)*

13 "The effects of various ginsenosides on calmodulin-dependent phosphodiesterase isozymes have been investigated. **Ginsenosides were found to be potent inhibitors of bovine heart calmodulin-dependent phosphodiesterase and the 60-kDa isozyme of bovine brain calmodulin-dependent phosphodiesterase**… These compounds therefore should be valuable tools to investigate the diverse physiological roles of distinct phosphodiesterase isozymes." *(Sharma RK, Kalra J. Ginsenosides are potent and selective inhibitors of some calmodulin-dependent phosphodiesterase isozymes. Biochemistry. 1993 May 18. 32(19). P 4975-8).*

14 "We studied the actions of saponin (ginsenosides) from Panax ginseng on free radical-induced pulmonary endothelial injury… Rb1 and Rg1 caused vasodilatation…. **These data indicate that GS may cause vasorelaxation and prevent manifestations of oxygen free radical injury by promoting release of nitric oxide.**" *(Kim H; Chen X; Gillis CN. Ginsenosides protect pulmonary vascular endothelium against free radical-induced injury. Biochem Biophys Res Commun. 1992 Dec 15. 189(2). P 670-6).*

15 "The effect of 18 kinds of Chinese herbal medicine for the synthesis of TXA2 and PGI2 was studied… **In this aspect they are better than the control drug (Aspirin) and other herbs of promoting blood circulation.**" *(Wang SR; Guo ZQ; Liao JZ. Experimental study on effects of 18 kinds of Chinese herbal medicine for synthesis of thromboxane A2 and PGI2. Chung Kuo Chung Hsi I Chieh Ho Tsa Chih. 1993 Mar. 13(3). P 167-70, 134).*

16 "**Rat brain microsomal Na+, K(+)-ATPase activity was inhibited significantly and rapidly by ginsenoside Rb1**… The inhibitory effect of Rg1 on rat brain microsomal Na+,K(+)-ATPase was much weaker than that of Rb1." *(Cao J; Zheng YQ; Liu TP; Feng LZ. Inhibitory effects of ginsenoside Rg1 and Rb1 on rat brain microsomal Na+,K(+)-ATPase activity. Chung Kuo Yao Li Hsueh Pao. 1990 Jan. 11(1). P 10-4).*

17 *Jia L, Zhao Y, Liang XJ. Current evaluation of the millennium phytomedicine- ginseng (II): Collected chemical entities, modern pharmacology, and clinical applications emanated from traditional Chinese medicine. Curr Med Chem. 2009;16(22):2924-42.*

18 "**Ginseng has been used for thousands of years in the East as a 'tonic', and in recent years its use has extended to Western society**…" *(Wilkie A, Cordess C. Ginseng:a root just like a carrot? J R Soc Med 1994; 87: 594-5).*

19 "Panax ginseng root powder is extensively used in the Far East for a wide variety of clinical ailments and to improve general physical and mental wellbeing. **It is now also being used in the Occident because of the adaptogenic activity of the plant**…." *(Mitra SK, Chakraborti A, Bhattacharya SK. Neuropharmacological studies on Panax ginseng. Indian J Exp Biol 1996; 34: 41-7).*

sportive[20]. L'azione farmacologica del Ginseng è estremamente varia e complessa, alcuni studi mostrano una possibile capacità nell'aumentare l'efficienza mentale e le capacità psicologiche e migliorare la sensazione di fatica mentale piuttosto che quella fisica[21]. Tale effetto sarebbe una diretta conseguenza della sua funzione di regolatore del glucosio nel sangue[22,23]. Tuttavia sono presenti in letteratura dei dati contrastanti in merito ad un miglioramento delle performance fisiche[24]. Di seguito alcuni studi clinici. In uno studio incrociato, in doppio cieco, controllato con placebo, 43 atleti di triathlon di alto livello hanno ricevuto per periodi di 10 settimane o un estratto standardizzato di Ginseng (200 mg/die) o il placebo. Si sono osservate differenze significative ($p<0,05$) in diversi parametri di resistenza solo dopo la seconda fase di trattamento. Si è concluso che il Ginseng ha migliorato la resistenza (resistenza allo stress di fine stagione), ma non ha migliorato la performance ottimale[25]. In uno studio randomizzato, in doppio cieco, 11 volontari sani maschi

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20 "**Ginseng has been used for several thousand years in the Orient as a tonic, prophylactic agent and 'restorative'… Ginseng has been used by athletes as an ergogenic aid for many years**, but there is an absence of compelling research evidence in support of its use for this purpose. Indeed, most of the support favouring the use of ginseng to enhance physical performance is of a testimonial nature." *(Bahrke MS, Morgan WP. Evaluation of the ergogenic properties of ginseng. Sports Med 1994; 18: 229-48).*

21 "Recent research has demonstrated that single doses of ginseng most notably engender cognitive benefits in terms of improved memory, but can also be associated with 'costs' in terms of attention task deficits following less mnemonically beneficial doses. A single dose of ginseng has also been shown to modulate cerebroelectrical (EEG) activity. It is suggested that ginseng would benefit from rigorous research further delineating its acute effects and exploring the relationship between acute effects and those seen during and following chronic administration regimens." *(Kennedy DO, Scholey AB.Ginseng: potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav. 2003 Jun;75(3):687-700.)*

22 "Single doses of the traditional herbal treatment Panax ginseng have recently been shown to elicit cognitive improvements in healthy young volunteers. The mechanisms by which ginseng improves cognitive performance are not known. However, they may be related to the glycaemic properties of some Panax species. Using a double-blind, placebo-controlled, balanced crossover design, 30 healthy young adults completed a 10 min test battery at baseline, and then six times in immediate succession commencing 60 min after the day's treatment (placebo, 200mg G115 or 400mg G115). The 10 min battery comprised a Serial Threes subtraction task (2 min); a Serial Sevens task (2 min); a Rapid Visual Information Processing task (5 min); then a 'mental fatigue' visual analogue scale. Blood glucose was measured prior to each day's treatment, and before, during and after the post-dose completions of the battery. Both the 200mg and 400mg treatments led to significant reductions in blood glucose levels at all three post-treatment measurements (p 0.005 in all cases). The most notable behavioural effects were associated with 200mg of ginseng and included significantly improved Serial Sevens subtraction task performance and significantly reduced subjective mental fatigue throughout all (with the exception of one time point in each case) of the post-dose completions of the 10 min battery (p 0.05). Overall these data suggest that Panax ginseng can improve performance and subjective feelings of mental fatigue during sustained mental activity. This effect may be related to the acute gluco-regulatory properties of the extract." *(Reay JL, Kennedy DO, Scholey AB .Single doses of Panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J Psychopharmacol. 2005 Jul;19(4):357-65.)*

23 "There was no evidence of a synergistic relationship between Panax ginseng and exogenous glucose ingestion on any cognitive outcome measure. Panax ginseng caused a reduction in blood glucose levels 1 hour following consumption when ingested without glucose. These results confirm that Panax ginseng may possess glucoregulatory properties and can enhance cognitive performance." *(Reay JL, Kennedy DO, Scholey AB. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. J Psychopharmacol. 2006 Nov;20(6):771-81.)*

24 *Barnes J. Anderson L.A. Phillipson J.D. Ginseng, Panax. Herbal Medicines. third ed. Pharmaceutical Press 2007:325-336.*

25 *Van Schepdael P. Les effets du ginseng G115 sur la capacité physique de sportifs d'endurance. Acta Ther 1993;19:337-47.*

per 8 settimane hanno ricevuto 200- 400 mg/die di un estratto di ginseng o il placebo. L'estratto non ha avuto alcun effetto su consumo di ossigeno, rapporto di scambio respiratorio, ventilazione al minuto, concentrazione di acido lattico nel sangue, frequenza cardiaca o sforzo percepito[26]. In un altro studio randomizzato, in doppio cieco, volontarie sane hanno ricevuto 200 mg/die di un estratto di Ginseng o placebo per lo stesso periodo. Il gruppo trattato con ginseng non ha mostrato miglioramenti su tutti i parametri della performance massimale (di lavoro, assorbimento di ossigeno a riposo, durante l'esercizio e nel recupero, sul rapporto di scambio respiratorio, sulla ventilazione al minuto, sulla frequenza cardiaca o sui livelli di acido lattico nel sangue). Gli effetti di un estratto standardizzato di Ginseng, sullo stato dell'umore e sulla risposta percettiva allo stress da esercizio submassimale e massimale, sono stati valutati in uno studio condotto su 19 giovani donne adulte che hanno ricevuto 200 mg/die di un estratto standardizzato di Ginseng radice o placebo[27]. I risultati riportati non supportano le affermazioni secondo le quali il ginseng migliorerebbe le caratteristiche delle funzioni psicologiche a riposo e durante lo stress da esercizio fisico. Il meccanismo dell'azione adattogena del Ginseng sembra essere principalmente di tipo neuro-endocrino, con coinvolgimento dell'asse ipotalamo-ipofisario e cortico-surrenalico.

L'azione dei ginsenosidi sarebbe, infatti, diretta prevalentemente sull'asse ipotalamo-ipofisi-surrene con aumento della produzione di glucocorticoidii (cosiddetti "ormoni dello stress"). L'attività di modulazione dei glucocorticoidi è stata dimostrata *in vitro* e *in vivo*[28,29]. Si osservano poi altri tipi di attività, alcune contrastanti con le azioni mediate dalla liberazione di glucocorticoidi, come ad esempio l'azione ipoglicemizzante. L'attività adattogena è stata dimostrata sperimentalmente nello

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26 *Engels H-J, Wirth JC. No ergogenic effects of ginseng (Panax ginseng C.A. Meyer) during graded maximal aerobic exercise. J Am Diet Assoc 1997;97:1110-5.*

27 *Engels H-J, Said JM, Wirth JC. Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. Nutr Res 1996;16:1295-305.*

28 "It has been established that glucocorticoid down-regulate GR. Ginsenosides (GSS) from extract of Panax ginseng have demonstrated glucocorticoid-like activities in homeostasis and regulation of immunity, ecc. We hypothesize that ginsenosides might mediate some of their actions by binding to the GR. We found that GSS alone had no effect on the expression of reporter gene, but it enhanced dexamethasone (Dex)-induced transcription of reporter gene. To further explore the effects of GSS, we examined the influence of GSS on the gene and protein expression as well as hormone binding activity of GR by semi-quantitative RT-PCR, Western blot, and radioligand-binding assay, respectively. GSS partially reversed the Dex-induced decrease in GR expression and hormone binding activity with an optimal dose of 25 microg/ml, implicating a positive regulatory effect of GSS on GR expression and binding activity." *(Ling C, Li Y, Zhu X, Zhang C, Li M.Ginsenosides may reverse the dexamethasone-induced down-regulation of glucocorticoid receptor. Gen Comp Endocrinol. 2005 Feb; 140(3):203-9.)*

29 "Male Sprague-Dawley rats were pretreated with saline (1 ml.d (-1)) or GSS (50 mg kg (-1).d (-1)) for 5 days, and then subjected to GR downregulation induced by polyvinyl alcohol containing hydrocortisone (F-PVA). Pretreatment with GSS resulted in upregulation of GR with respect to binding capacity, cytoplasmic protein expression, and mRNA levels, but did not produce significant effects on GR binding affinity and serum corticosterone levels. Pretreatment with GSS also led to increase in GR translocation and TAT mRNA levels. Data obtained in the present study indicate that GSS may upregulate GR levels IN VIVO and enhance glucocorticoid efficiency." *(Binbin C, Yinglu F, Juan D, Changquan L.Upregulation effect of ginsenosides on glucocorticoid receptor in rat liver. Horm Metab Res. 2009 Jul;41(7):531-6.)*

stress da freddo e nel nuoto forzato[30].

Nel topo, la somministrazione di *Ginseng Radix, Epimedii Herba* e *Agkistrodon Japonicae* alla dose di 0,1 ml/10 g, aumenta la capacità natatoria dell'animale e riduce il tempo d'immobilità da tetrabenazina[31].

Un trial clinico condotto in doppio cieco e controllato, conferma l'attività del *Panax ginseng* nel migliorare la qualità della vita di 625 pazienti di entrambi i sessi, di entità superiore rispetto ad altri supplementi dietetici[32].

Una sperimentazione clinica condotta in doppio cieco, ha dimostrato che un supplemento dietetico con *Panax ginseng*, dimetilaminoetanolo bitartrato, vitamine e minerali, aumenta la capacità di lavoro di volontari sani al treadmill test. Negli stessi soggetti si osserva una riduzione del consumo di ossigeno, della ventilazione, della concentrazione plasmatica di acido lattico, della produzione di anidride carbonica e della frequenza cardiaca. L'effetto è maggiormente evidente nei soggetti poco allenati, con un consumo massimo di ossigeno sotto sforzo inferiore ai 60 ml/kg/min[33]. In due trial clinici in doppio cieco, controllati e con il placebo, in volontari sani adulti è stata somministrata una associazione di estratti di *Panax Ginseng* e *Ginkgo biloba*, per periodi massimo di dodici settimane, i risultati ottenuti mostrano un miglioramento delle capacità cognitive e della memoria rispetto ai

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30 "A new animal model for evaluating improvement in physical work performance and endurance in an adverse environment is described… **Panax ginseng root and Ginkgo biloba leaf extracts were compared for their positive endurance-promoting properties using both models.**" *(Ramachandran U, Divekar HM, Grover SK, Srivastava KK. New experimental model for the evaluation of adaptogenic products. J Ethnopharmacol 1990; 29: 275-81).*

31 "The aim of the present study was to clarify acute anti-fatiguing effects of three crude liquid drug preparations (S1-S3), containing almost the same amounts of *Ginseng Radix, Epimedii Herba and Agkistrodon Japonicae*… **These results indicate that these crude preparations may cause tonic effects and so far tested, these effects seem to be more effective on subjects fatigued with physical and/or mental works than an normal subjects.**" *(Tadano T, Aizawa T, Asao T, Hozumi M, Kisara K. Pharmacological studies of nutritive and tonic crude drugs on fatigue in mice. Nippon Yakurigaku Zasshi 1992; 100: 423-31).*

32 "To remedy the deterioration in quality of life in large cities, the addition of ginseng root extract to a multivitamin base appears to produce a promising dietary supplement. The aim of the present study was tocompare the quality-of-life parameters in subjects receiving multivitamins plus ginseng with those found in subjects receiving multivitamins alone. The study was comparative, randomized and double-blind, and it involved 625 patients of both sexes divided into two groups taking one capsule per day for 12 weeks… **This study has demonstrated that ginseng extract G115 Pharmaton Capsules were more effective than the multivitamin capsules alone in improving the quality-of-life in a population subjected to the stress of high physical and mental activity.**" *(Caso Marasco A, Vargas Ruiz R, Salas Villagomez A, Begona Infante C. Double-blind study of a multivitamin complex supplemented with ginseng extract. Drugs Exp Clin Res 1996;. 22: 323-9).*

33 "The subjects of this double-blind, randomized, crossover study were 50 healthy male sports teachers aged 21 to 47 years. Every day for six weeks each subject received two capsules of a preparation containing ginseng extract, dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements, or two capsules of placebo…**The effects of ginseng were more pronounced in the subjects with maximal oxygen consumption below 60 ml/kg/min during exercise than in the subjects with levels of 60 ml/kg/min or above. The results indicate that the ginseng preparation increased the subjects' work capacity by improving muscular oxygen utilization.**" *(Pieralisi G, Ripari P, Vecchiet L. Effects of a standardized ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals, and trace elements on physical performance during exercise. Clin Ther 1991; 13: 373-82).*

controlli[34,35].

Attività antiamnesica. Numerosi AA. riferiscono un'attività dell'estratto di *Panax ginseng* sull'apprendimento e sul consolidamento della memoria nel ratto anziano, e in numerosi modelli sperimentali di amnesia. L'effetto è comparabile a quello ottenuto con specifici farmaci nootropi[36]. L'effetto è confermato in ratti giovani, con l'impiego di ginsenosidi di *Panax ginseng* alla dose di 10-50 mg/kg p.o. in somministrazione ripetuta per 7 giorni[37]. Gli animali mostrano un evidente miglioramento delle capacità di apprendimento e di memorizzazione; in particolare, il *Panax ginseng* antagonizza i deficit della memoria recente e della memoria remota, indotti, rispettivamente, da

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34 "The effects of capsules containing 60 mg of a standardised extract of Ginkgo biloba (GK501) and 100 mg of a standardised extract of Panax ginseng (G115) on various aspects of cognitive function were assessed in healthy middle-aged volunteers. A double blind, placebo controlled, 14 week, parallel group, repeated assessment, multi-centre trial of two dosing regimens, 160 mg b.i.d. and 320 mg o.d. was conducted. Two hundred and fifty-six healthy middle-aged volunteers successfully completed the study. On various study days (weeks 0, 4, 8, 12 and 14) the volunteers performed a selection of tests of attention and memory from the Cognitive Drug Research computerised cognitive assessment system prior to morning dosing and again, at 1, 3 and 6 h later. The volunteers also completed questionnaires about mood states, quality of life and sleep quality. The Ginkgo/ginseng combination was found significantly to improve an Index of Memory Quality, supporting a previous finding with the compound. This effect represented an average improvement of 7.5% and reflected improvements to a number of different aspects of memory, including working and long-term memory. This enhancement to memory was seen throughout the 12-week dosing period and also after a 2-week washout. This represents the first substantial demonstration of improvements to the memory of healthy middle-aged volunteers produced by a phytopharmaceutical." *(Wesnes KA, Ward T, McGinty A, Petrini O.The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle-aged volunteers. Psychopharmacology (Berl). 2000 Nov;152(4):353-61.)*

35 "...In each double-blind, placebo-controlled study three different treatment doses and a placebo were administered, according to a balanced crossover design, with a 7-day washout period between each dose. Participants' scores on two computerised serial subtraction tasks (Serial Threes and Serial Sevens) were assessed pre-dosing and at 1, 2.5, 4 and 6 h thereafter. A number of significant time, dose and task-specific effects were associated with each treatment. There was a dose-dependent improvement in speed of responding during Serial Threes following Ginkgo biloba. Different doses of Ginseng improved accuracy and slowed responses during Serial Sevens. The most striking result, however, was a highly significant and sustained increase in the number of Serial Sevens responses following 320 mg of the Ginkgo-Ginseng combination at all post-treatment testing times. " (*Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand. Hum Psychopharmacol. 2002 Jan;17(1):35-44.)*

36 "In experiments of 2-, 5-, 10- and 22-month old rats, using active avoidance with punishment reinforcement (maze and shuttle-box) and passive avoidance (step-down), we found that acquisition and retention in aged rats were impaired significantly or only as a trend. **The nootropics adafenoxate, meclofenoxate, citicholine, aniracetam and the standardized ginseng extract administered orally for 7 to 10 days usually facilitated learning and improved memory in the rats of all ages.**" *(Petkov VD, Mosharrof AH, Petkov VV, Kehayov RA. Age-related differences in memory and in the memory effects of nootropic drugs. Acta Physiol Pharmacol Bulg 1990; 16: 28-36).*

37 "**The present investigation has shown that Ginseng root saponins (ig, 50mg/kg x 7d) facilitate the learning and memory of normal male Wistar rats**, while the effect of Ginseng stem-leaf saponins (ig, 50mg/kg x 7d) on antielectrconvulsive shock-induced impairment of memory consolidation in rats is more intensive than that of root saponins." *(Wang A, Cao Y, Wang Y, Zhao R, Liu C. Effects of Chinese ginseng root and stem-leaf saponins on learning, memory and biogenic monoamines of brain in rats. Chung Kuo Chung Yao Tsa Chih 1995; 20: 493-5).*

scopolamina[38] e cicloeximide[39]; le amnesia da ischemia cerebrale[40]; le amnesie del ratto anziano[41]. I ginsenosidi antagonizzano anche i deficit della memoria indotti da agenti antiserotoninergici[42]. L'effetto sembra dovuto prevalentemente al ginsenoside Rb1[43], che non ha alcun effetto né sui recettori dell'acetilcolina (ACh) né sull'attività dell'acetilcolinesterasi, ma aumenta la liberazione di ACh dai neuroni dell'ippocampo[44]. Inoltre, quando somministrato per 3 giorni nel ratto, il ginsenoside Rb1 ha dimostrato di accelerare l'uptake della colina – il principale precursore dell'acetilcolina – nei

[38] "The effects of Panax ginseng ethanol extract and its water (WSF)- and lipid-soluble (LSF) fractions on the scopolamine-induced disruption of radial maze performance in rats were examined. Ginseng root was refluxed with ethanol, and WSF and LSF were prepared from this ethanol extract. Scopolamine (0.075-0.3 mg/kg, i.p.) dose-dependently impaired the maze performance. However, **the oral administration of Panax ginseng ethanol extract and WSF (2-8 g dried root/kg) 90 min before testing improved the maze performance** disrupted by scopolamine (0.3 mg/kg) in a dose-dependent manner, but LSF failed to attenuate the disruption. These data suggest that **ginseng extract possesses a beneficial effect regarding spatial cognitive impairment and that the water-soluble fraction of ginseng extract mainly contributes to the effect of the ethanol extract.**" *(Nitta H, Matsumoto K, Shimizu M, Ni XH, Watanabe H. Panax ginseng extract improves the scopolamine-induced disruption of 8-arm radial maze performance in rats. Biol Pharm Bull 1995; 18: 1439-42).*

[39] "Using a multiple-trial, training-to-criterion procedure, the effects of repeated administrations of ginseng stem-leaves saponins (GSLS) on learning and memory of one-way avoidance in rats were studied in shuttle-box… **The results indicate that GSLS facilitated the acquisition of learning and memory in rats, and improved the scopolamine amnesia and cycloheximide amnesia.**" *(Ma TC, Yu QH, Chen MH. Effects of ginseng stem-leaves saponins on one-way avoidance behavior in rats. Chung Kuo Yao Li Hsueh Pao 1991; 12: 403-6).*

[40] "The present study was designed to investigate the possible neuroprotective activity of ginseng roots in 5-min ischemic gerbils using a step-down passive avoidance task and subsequent neuron and synapse counts in the hippocampal CA1 region… Ginsenoside Rb1 significantly prolonged the response latency of ischemic gerbils and rescued a significant number of ischemic CA1 pyramidal neurons… **These findings suggest that RGP and CGS are effective in the prevention of delayed neuronal death, and that ginsenoside Rb1 is one of the neuroprotective molecules within ginseng root.**" *(Wen TC, Yoshimura H, Matsuda S, Lim JH, Sakanaka M. Ginseng root prevents learning disability and neuronal loss in gerbils with 5-minute forebrain ischemia. Acta Neuropathol 1996; 91: 15-22).*

[41] "The effect of Panax ginseng extract on the learning performance of aged Fischer 344 rats using the 8-arm radial maze task and the operant discrimination task was examined… **These results suggest that subchronic treatment with ginseng extract improves spatial cognitive impairment in aged rats.**" *(Nitta H, Matsumoto K, Shimizu M, Ni XH, Watanabe H. Panax ginseng extract improves the performance of aged Fischer 344 rats in radial maze task but not in operant brightness discrimination task. Biol Pharm Bull1995; 18: 1286-8).*

[42] "The effects of 20(S)-ginsenoside-Rg2 (GRg2, CAS 52286-74-5) and cyproheptadine (CYP, CAS 129-03-3) on acquisition, retention and retrieval were examined in male Wistar rats… **The results also provide the suggestive evidence that central serotonin may play a positive modulatory role in the acquisition, retention and retrieval of two-way active avoidance responding in rats.**" *(Ma TC; Yu QH. Effect of 20(S)-ginsenoside-Rg2 and cyproheptadine on two-way active avoidance learning and memory in rats. Arzneimittelforschung 1993; 43: 1049-52).*

[43] The effects of ginsenosides Rg1, Rd and Rb1 on impaired performance induced in the rat by scopolamine were examined in a radial-arm maze… **It is suggested that cholinergic neurons in the medial septum are involved in the ameliorative effect of Rg1 on impaired performance induced by scopolamine.**" *(Yamaguchi Y, Haruta K, Kobayashi H. Effects of ginsenosides on impaired performance induced in the rat by scopolamine in a radial-arm maze. Psychoneuroendocrinology 1995; 20: 645-53).*

[44] "Ginsenosides, the saponins of ginseng, are bioactive ingredients which exert many beneficial effects. One ginsenoside, Rb1… partially prevents the memory deficits induced by a cholinergic agent (scopolamine) in rats… **The ability of Rb1 to prevent memory deficits may be related to facilitation of ACh metabolism in the central nervous system.**" *(Benishin CG, Lee R, Wang LC, Liu HJ. Effects of ginsenoside Rb1 on central cholinergic metabolism. Pharmacology 1991; 42: 223-9).*

neuroni colinergici[45]. Recenti studi hanno messo in evidenza un effetto stimolante dei ginsenosidi sulla colina acetiltransferasi (ChAT), l'enzima che sintetizza l'ACh a partire dalla colina[46], e sulla "long-term potentiation"[47], un meccanismo elettrochimico che consente la fissazione della memoria a lungo termine nell'ippocampo. È da notare che l'effetto sulla ChAT è direttamente proporzionale all'effetto antiamnesico dei ginsenosidi, sia nel ratto giovane sia in quello anziano[48].

Un interessante lavoro ha dimostrato che la somministrazione di Rb1 o Rg1, alla dose di 28-56 mg/kg, a topolini durante l'allattamento, accelera lo sviluppo e la maturazione del sistema nervoso centrale. In particolare, le sinapsi dei neuroni ippocampali della regione CA3 – quella più direttamente coinvolta nei processi di apprendimento e di memorizzazione – appaiono più numerose negli animali trattati con ginsenosidi che negli animali di controllo[49]. Su questi neuroni, i ginsenosidi hanno anche un'attività protettiva nei confronti di aminoacidi eccitatori[50] e dell'ipossia cerebrale[51], che potrebbe spiegare gli effetti del *Panax ginseng* sull'invecchiamento cerebrale. L'effetto

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45 "The ginsenoside Rb1 has previously been reported to improve memory deficits induced by anticholinergic drug treatment, and to facilitate acetylcholine (Ach) release from rat brain hippocampal slices… In the present studies, **analysis of choline uptake kinetics indicated that Rb1 increased the maximum velocity of choline uptake,** while the affinity of the choline uptake carrier for choline (Km) was not significantly altered… **chronic (3 day) administration of Rb1 did increase the number of choline uptake sites in the hippocampus, and to a lesser extent in the cortex.**" *(Benishin CG. Actions of ginsenoside Rb1 on choline uptake in central cholinergic nerve endings. Neurochem Int 1992; 21: 1-5).*

46 "Ginsenoside Rb1 (Rb1), a saponin of North American ginseng (Panax quinquefolium L.), has been found to exert beneficial effects on memory and learning, putatively through its actions on the cholinergic system… **These findings support the specificity of the effects of Rb1 on certain aspects of the cholinergic and neurotrophic systems.**" *(Salim KN; McEwen BS; Chao HM. Ginsenoside Rb1 regulates ChAT, NGF and trkA mRNA expression in the rat brain. Brain Res Mol Brain Res 1997; 47: 177-82).*

47 "Ginseng saponins are known to have various pharmacological actions on the central nervous system. In the present study, we investigated the effects of ginsenoside Rb1 (GRb1) and malonylginsenoside Rb1 (GRb1-m) on the induction of long-term potentiation (LTP) in the dentate gyrus using anesthetized rats… **This is the first report providing direct evidence that ginseng saponins affect the activity-dependent synaptic plasticity in the brain.**" *(Abe K, Cho SI, Kitagawa I, Nishiyama N, Saito H. Differential effects of ginsenoside Rb1 and malonylginsenoside Rb1 on long-term potentiation in the dentate gyrus of rats. Brain Res 1994; 649: 7-11).*

48 "In young adult rats with scopolamine-induced cognitive impairment, choline acetyltransferase activity was increased in the medial septum, but not in the diagonal band, caudate and hippocampus, 30 min after the injection of ginsenosides Rg1 or Re… **These results suggest that Rg1 and Re may contribute the ameliorative effects through an increase of choline acetyltransferase activity in the medial septum.**" *(Yamaguchi Y, Higashi M, Kobayashi H. Effects of ginsenosides on maze performance and brain choline acetyltransferase activity in scopolamine-treated young rats and aged rats. Eur J Pharmacol 1997; 329: 37-41).*

49 "Weaning mice were supplied drinking water containing Rb1 or Rg1 0.125 or 0.25 mg.ml-1 for 4 weeks. Rb1 (28.6 and 56.1 mg.kg-1) and Rg1 (27.4 and 53.9 mg.kg-1) were found to accelerate young mice body and brain development as well as facilitate memory acquisition in step down and step through avoidance response tests… **This is the morphological basis for explaining Rb1 and Rg1 induced facilitation of learning and memory.**" *(Ying Y, Zhang JT, Shi CZ, Qu ZW, Liu Y. Study on the nootropic mechanism of ginsenoside Rb1 and Rg1:influence on mouse brain development. Yao Hsueh Hsueh Pao 1994; 29: 241-5).*

50 "It has been well documented that ginsenoside Rb1 and Rg1 are important active principles of ginseng… The results showed that Rb1 and Rg1 could selectively inhibit the high level glutamate (500 mumol.L-1) induced increase of [Ca2+]i, suggesting that **the neuroprotective activities of Rb1 and Rg1 were mediated by blocking calcium over-influx into neuronal cells.**" *(Liu M, Zhang JT. Protective effects of ginsenoside Rb1 and Rg1 on cultured hippocampal neurons. Yao Hsueh Hsueh Pao 1995; 30: 674-8).*

51 "To study cerebral protective mechanism of Panax notoginseng saponins (PNS)… **The protection against hypoxic damage**

è particolarmente evidente con il ginsenoside Rb1[52].

Ricerche condotte per chiarire il meccanismo di azione antiamnesica dei ginsenosidi Rg1 ed Rb1, evidenziano l'assenza di legame dei due composti ai recettori α1, α2, β1, DA, 5-HT, GABA e muscarinici. Al contrario, i due composti sembrano stimolare la sintesi di proteine ed elevare i contenuti intracerebrali di ACTH[53]. Recentemente molti studi sono stati condotti per indagare un eventuale legame tra il ginseng e la malattia di Alzheimer e i risultati che ne sono emersi sono spesso controversi e inconclusivi. Uno studio condotto su pazienti malati di Alzheimer e trattati per 12 settimane con ginseng oppure placebo ha mostrato una significativa differenziazione nelle capacità cognitive e mnemoniche nei pazienti trattati con estratto di ginseng concludendo perciò che il ginseng è clinicamente utile nel migliorare le capacità cognitive di malati affetti da Alzheimer [54]. Uno studio del 2009 ha indagato la funzione del ginsenoside Rg3, uno dei principali ginsenosidi presenti nell'estratto, come riduttore del livello del peptide beta-Amiloide nel cervello, responsabili dell'insorgenza della malattia ed è stato riconfermato che il Ginseng può essere utile nel trattamento di malati di Alzheimer[55]. Tuttavia, data la delicatezza della questione sono necessari

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of PNS was related to improving energy metabolism, preserving the structural integrity of neurons." *(Jiang KY, Qian ZN.. Effects of Panax notoginseng saponins on posthypoxic cell damage of neurons in vitro. Chung Kuo Yao Li Hsueh Pao 1995; 16: 399-402).*

52 "The present study demonstrated that the intracerebroventricular infusion of ginsenoside Rb1 after 3.5 min or 3 min forebrain ischemia, precluded significantly the ischemia-induced shortening of response latency in a step-down passive avoidance task and rescued a significant number of hippocampal CA1 neurons from lethal ischemic damage… These findings suggest that the central infusion of ginsenoside Rb1 after forebrain ischemia protects hippocampal CA1 neurons against lethal ischemic damage possibly by scavenging free radicals which are overproduced in situ after brain ischemia and reperfusion. **The present study may validate the empirical usage of ginseng root over thousands of years for the prevention of cerebrovascular diseases**" *(Lim JH, Wen TC, Matsuda S, Tanaka J, Maeda N, Peng H, Aburaya J, Ishihara K, Sakanaka M. Protection of ischemic hippocampal neurons by ginsenoside Rb1, a main ingredient of ginseng root. Neurosci Res 1997; 28: 191-200).*

53 "The effect of ginsenoside Rg1 and Rb1 on memory in mice and rats were studied using one trial avoidance learning method. The results showed that **Rg1 and Rb1 improved acquisition, consolidation and retrieval of memory improved by amnestic agents**… Rg1 and Rb1 were shown to increase protein biosynthesis of brain and ACTH level of plasma and decrease 5-HT level or slow down the 5-HT turnover rate in rats. No specific binding of Rg1 and Rb1 to α1, α2 and β-adrenoceptors, or to DA, 5-HT, GABA and M-cholinergic receptors was detectable… Clearly, these data may serve as the basis for the elucidation of the antiamnestic mechanism of Rg1 and Rb1" *(Zhang JT, Qu ZW, Liu Y, Deng HL. Preliminary study on antiamnestic mechanism of ginsenoside Rg1 and Rb1. Chin Med J 1990; 103: 932-8).*

54 "We investigated the clinical efficacy of Panax ginseng in the cognitive performance of AD patients in an open-label study. Consecutive AD patients were randomly assigned to the ginseng (n=58) or the control group (n=39), and the ginseng group was treated with Panax ginseng powder (4.5 g/d) for 12 weeks. Cognitive performances were monitored using the mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS) during 12 weeks of the ginseng treatment and at 12 weeks after the ginseng discontinuation. MMSE and ADAS scales showed no baseline difference between the groups. After ginseng treatment, the cognitive subscale of ADAS and the MMSE score began to show improvements and continued up to 12 weeks (P=0.029 and P=0.009 vs. baseline, respectively). After discontinuing ginseng, the improved ADAS and MMSE scores declined to the levels of the control group. These results suggest that Panax ginseng is clinically effective in the cognitive performance of AD patients." *(Lee ST, Chu K, Sim JY, Heo JH, Kim M.Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord. 2008 Jul-Sep;22(3):222-6.*).

55 "In this study, we investigated the effect of ginsenoside Rg3, one of the major active components of ginseng, on the metabolism of Abeta40 and Abeta42 in SK-N-SH cells transfected with Swedish mutant beta-amyloid precursor protein (SweAPP). The ELISA result showed that Rg3 significantly reduced the levels of Abeta40 and Abeta42, 19.65 +/- 6.05%, 23.61 +/- 6.74%, respectively

molti altri studi e molto più accurati per poter affermare con certezza che il Ginseng possiede una importante funzione nel contrastare la malattia di Alzheimer [56.]

Altri effetti sul sistema nervoso centrale e periferico. Diversi studi hanno recentemente descritto gli effetti benefici del Ginseng e dei suoi componenti in diverse malattie neurodegenerative. Un particolare interesse ha suscitato il morbo di Parkinson. Uno studio in vivo ha riportato che un uso prolungato dell'estratto di Ginseng protegge dagli effetti neurotossici provocati dal morbo di Parkinson[57]. L'estratto di *Panax ginseng* prolunga la vitalità di neuroni cerebrali coltivati in vitro: l'effetto sembra specifico del ginsenoside Rb1, e assente per altri ginsenosidi[58]. Recentemente molti sono studi confermano un effetto neuroprotettivo dei ginsenosidi[59,60,61]. Il ginsenoside Rd sembra avere un effetto protettivo sui neuroni dell'ippocampo, inibendo la morte cellulare, potrebbe essere

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(P < 0.01). The Western blot analysis showed that Rg3 reduced the levels of Abeta40 and Abeta42 through enhancing NEP gene expression, and real-time PCR assay showed that 50 microM Rg3 could significantly enhance NEP gene expression (2.9 fold at 48 h). Our findings suggest that the Rg3 compound of ginseng may be useful for treating patients suffering with Alzheimer's disease." *(Yang L, Hao J, Zhang J, Xia W, Dong X, Hu X, Kong F, Cui X.Ginsenoside Rg3 promotes beta-amyloid peptide degradation by enhancing gene expression of neprilysinJ Pharm Pharmacol. 2009 Mar;61(3):375-80.)*

56 *Lee MS, Yang EJ, Kim JI, Ernst E.Ginseng for cognitive function in Alzheimer's disease: a systematic review. J Alzheimers Dis. 2009;18(2):339-44.*

57 *Van Kampen J, Robertson H, Hagg T, Drobitch R. Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease. Exp Neurol 2003; 184:21–29).*

58 "The effects of nerve growth factor (NGF) and saponins isolated from Panax ginseng C.A. Mayer on the survival of chick and rat embryonic cerebral cortex neurons were examined. **Ginsenoside Rg1 (GRg1) exerted a survival-promoting effect on both chick and rat cerebral cortex neurons in cell cultures.** Ginsenoside Rb1 (GRb1) also had an effect in the rat and displayed some influence in the chick." *(Himi T, Saito H, Nishiyama N. Effect of ginseng saponins on the survival of cerebral cortex neurons in cell cultures. Chem Pharm Bull 1989; 37: 481-4).*

59 "..we have identified ginsenosides Rb1 and Rg1, extracted from ginseng root (Panax ginseng C. A. Meyer), as efficient neuroprotective agents for spinal cord neurons. These compounds protect spinal neurons from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by H(2)O(2). The neuroprotective effects are dose-dependent. The optimal doses are 20-40 microM for ginsenosides Rb1 and Rg1. The effects are specific for Rb1 and Rg1, since a third ginsenoside, Re, did not exhibit any activity. Ginseng has been used for thousands of years in the treatment of neurological disorders and other diseases in Asia. Ginsenosides Rb1 and Rg1 represent potentially effective therapeutic agents for spinal cord injuries." *(Liao B, Newmark H, Zhou R. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. Exp Neurol. 2002 Feb; 173(2):224-34.)*

60 *Rausch WD, Liu S, Gille G, Radad K. Neuroprotective effects of ginsenosides. Acta Neurobiol Exp (Wars). 2006;66(4):369-75.*

61 "Ginsenoside Rg2 significantly attenuated glutamate-induced neurotoxic effects upon these parameters at all doses tested. Our study suggests that ginsenoside Rg2 has a neuroprotective effect against glutamate-induced neurotoxicity through mechanisms related to anti-oxidation and anti-apoptosis. In addition, the inhibitory effect of ginsenoside Rg2 against the formation of Abeta1-40 suggests that ginsenoside Rg2 may also represent a potential treatment strategy for Alzheimer's disease. " (*Li N, Liu B, Dluzen DE, Jin Y. Protective effects of ginsenoside Rg2 against glutamate-induced neurotoxicity in PC12 cells. J Ethnopharmacol. 2007 May 22; 111(3):458-63.)*

perciò un utile aiuto nella protezione contro ischemie cerebrali[62,63]. In vivo, alla dose di 200 mg/kg, le saponine triterpeniche del *Panax ginseng* prevengono l'aumento della temperatura corporea e delle concentrazioni intracerebrali di corticosteroidi nello stress da caldo nel topo; nello stesso modello sperimentale, il *Panax ginseng* antagonizza la riduzione dei contenuti di serotonina e noradrenalina nel tessuto cerebrale[64]. Alla posologia di 100 mg/kg/die per 7 settimane, l'estratto di *Panax ginseng* riduce il metabolismo della serotonina, della dopamina e della noradrenalina in aree specifiche del sistema nervoso centrale, e riduce l'attività motoria del topo[65]. Secondo alcuni AA., l'effetto del *Panax ginseng* sulla motilità spontanea sarebbe diverso con l'età: inibitorio nel ratto giovane, e stimolante nel ratto anziano, la cui motilità spontanea sarebbe patologicamente ridotta con l'età[66]. Infine, alcune ricerche sembrano indicare un'attività protettiva del *Panax ginseng*

62 "Ethanolic P. ginseng extract (200 mg/kg, i.p.) significantly protected CA1 neurons against 10 minutes of transient forebrain ischemia as demonstrated by measuring the density of neuronal cells. P. ginseng also significantly decreased the level of MDA and increased the expression of GPx and SOD. These results suggest that P. ginseng might be neuroprotective against cerebral ischemia-induced injury in rat brain by decreasing lipid peroxides and increasing the expression of GPx and SOD." *(Kim YO, Kim HJ, Kim GS, Park HG, Lim SJ, Seong NS, Ham YW, Lee SD, Jang KH, Jung KH, Chung JH, Kang SA Panax ginseng protects against global ischemia injury in rat hippocampus. J Med Food. 2009 Feb; 12(1):71-6.)*

63 "We previously found that ginsenoside Rd (GSRd), one of the main active ingredients in Panax Ginseng, attenuates H(2) O(2)-induced oxidative injury in PC12 cells. Mounting evidence suggests that the oxidative stress is crucially involved in the pathophysiologic process of ischemia. In the present study, we examined the protective role of GSRd to attenuate ischemic neuronal injury in vitro. Cultured hippocampal neurons were exposed to oxygen-glucose deprivation (OGD) for 2h followed by a 24-h reoxygenation. GSRd exhibited remarkable neuroprotection when presented during OGD and reoxygenation, which may be ascribed to its antioxidative properties by reducing the intracellular reactive oxygen species and malondialdehyde production; increasing glutathione content; and enhancing the antioxidant enzymatic activities of catalase, superoxide dismutase and glutathione peroxidase. Additionally, GSRd could stabilize the mitochondrial membrane potential and attenuate apoptotic death of hippocampal neurons after OGD exposure." (*Ye R, Li N, Han J, Kong X, Cao R, Rao Z, Zhao G Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. Neurosci Res. 2009 Jul; 64(3):306-10.)*

64 "The rectal temperature and serum corticosterone increased in mice exposed to 45°C for 15 min; at the same time, the contents of brain 5-HT and NE reduced, brain DA unchanged. **Ginseng root saponins (GRS) ip 200 mg/kg inhibited the increase of serum corticosterone and the decrease of brain 5-HT and NE in heat-stressed mice**, but did not affect brain DA. GRS lowered mice body temperature at room temperature and inhibited the rise of body temperature under heat environmental conditions in mice… PCPA eliminated only the inhibition of GRS on hyperthermia under heat-stress, but had no significant effect on hypothermia at room temperature." *(Yuan WX, Wu XJ, Yang FX, Shang XH, Zhang LL. Effects of ginseng root saponins on brain monoamines and serum corticosterone in heat-stressed mice. Chung Kuo Yao Li Hsueh Pao 1989; 10: 492-6).*

65 "Effects of the Panax ginseng root (PGR) on spontaneous motor activity (vertical and horizontal motor activities), and on monoamine-related substances (tyrosine, DA, DOPAC, 3-MT, HVA, NE, MHPG, tryptophan, 5-HT, and 5-HIAA) in discrete brain areas (cerebral cortex, hippocampus, hypothalamus, corpus striatum, limbic lobe, midbrain, cerebellum, and medulla oblongata) of ddY male mice (weighing 18-22 g) were examined using an infrared photo-cell counter and HPLC with electrochemical detection… **These results show that PGR exerts an influence on the CNS.**" *(Itoh T, Zang YF, Murai S, Saito H. Effects of Panax ginseng root on the vertical and horizontal motor activities and on brain monoamine-related substances in mice. Planta Med 1989; 55: 429-33).*

66 "Effects of Panax ginseng on the spontaneous motor activity and central dopaminergic systems in old rats were investigated and compared with those in young rats… **These results suggest that subchronic intake of ginseng extract inhibits the activity of nigro-striatal dopamine neurons in the daytime and activates spontaneous motor activity during the dark period in old rats, while it produces opposite effects in young rats."** *(Watanabe H, Ohta H, Imamura L, Asakura W, Matoba Y, Matsumoto K.. Effect of Panax ginseng on age-related changes in the spontaneous motor activity and dopaminergic nervous system in the rat. Jpn J Pharmacol 1991; 55: 51-6).*

nei confronti della tossicità fetale di etanolo[67] o di altre sostanze che possano in qualche modo rallentare o danneggiare lo sviluppo embrionale e fetale.

Attività immunostimolante. L'attività immunostimolante del *Panax ginseng* è documentata in letteratura da una vasta bibliografia, generalmente di buona qualità e affidabile. I ginsenosidi stimolano in vitro l'attività dei macrofagi[68] e la mitogenesi dei linfociti B eT[69], e sembrano avere un ruolo di regolazione nella liberazione di neurochinina (NK), interferone (INF) ed interleuchina-1 (IL-1)[70], e nelle loro reciproche interazioni. L'effetto è evidente anche su linfociti umani, la cui proliferazione in presenza di una stimolazione antigenica è aumentata dal ginsenoside Rg1; l'effetto immunostimolante è maggiore sui linfociti di soggetti anziani, e nelle condizioni di depressione della funzionalità leucocitaria[71].

I ginsenosidi agirebbero in senso immunostimolante con un meccanismo di azione postrecettoriale, regolando i livelli intracellulari di cAMP e cGMP[72]. Nel ratto anziano questo porterebbe ad una

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67 "This study was performed to determine the active constituents of the root of Panax ginseng C. A. Mayer in the amelioration of ethanol-induced impediment of brain growth in the neonatal stage… **A saponin fraction of ginseng extract prevented this ethanol-induced reduction of brain weight. Some ginseng saponins including ginsenosides Rg1, Rb2, Rd, Rf and Re effected stimulated a potent recovery of cerebellum growth in this animal model.**" *(Okamura N, Kobayashi K, Akaike A, Yagi A. Protective effect of ginseng saponins against impaired brain growth in neonatal rats exposed to ethanol. Biol Pharm Bull 1994; 17: 270-4).*

68 "This study investigated the effect of a dried ginseng extract on polymorphonuclear leucocytes (PMNL) in bovine blood and milk. In a test for chemiluminescence (CL), PMNL were pre-incubated in ginseng solution at 37 °C in 5% CO2 for 60 min, and then stimulated with bovine serum opsonized zymosan… **The proportion of actively phagocytic cells in the ginseng-treated group was greater than that in the non-ginseng treated group."** *(Hu S, Concha C, Cooray R, Holmberg O. Ginseng-enhanced oxidative and phagocytic activities of polymorphonuclear leucocytes from bovine peripheral blood and stripping milk. Vet Res 1995; 26: 155-61).*

69 "**Ginseng (GS), the root of Panax ginseng CA Meyer, has been used in China for thousands of years to enhance the body's resistance to many diseases.** In the present study, a dry ginseng extract was investigated to evaluate its immunomodulating effects in vitro on the peripheral blood and stripping milk lymphocytes. **The response was significantly augmented (approximately 20%) in the peripheral blood lymphocytes incubated with GS extract in combination with PWM, as compared with the cells incubated with PWM alone**…" *(Concha C, Hu S, Holmberg O. The proliferative responses of cow stripping milk and blood lymphocytes to pokeweed mitogen and ginseng in vitro. Vet Res 1996; 27: 107-15).*

70 "Effect of panaxatriol ginsenoside (PG) on interleukin-1 (IL-1) gene expression was studied by using wheat germ extract (cell-free translation system) and IL-1 bioassay. **The results showed that IL-1 production increased by 40% (487-682 U/ml) at maximum during cell culture (0-84 h) after PG (10 µg/ml) was added** to phytohemagglutinin (PHA, 50 µg.ml-1) stimulated lymph node cells…" *(Tian ZG, Yang GZ. Promoting effect of panaxatriol ginsenoside on gene expression of human interleukin-1. Chung Kuo Yao Li Hsueh Pao 1993; 14:159-61).*

71 "We used the saponin Rg1 extracted from Panax ginseng to study its effects on lymphocytes of 10 young and 19 elderly persons. The proliferative response of lymphocytes cocultured for 72 h with PHA and saponin was measured by using MTT method and the 3H-TdR incorporation procedure. PHA and Rg1 had stimulative effects on the phenotype of lymphocytes ($P < 0.001$). Rg1 also increased the fluidity of lymphocyte membrane of the aged ($P < 0.001$). The CD25 and CD45RA positive cells of lymphocytes in the elderly were lower than those of the young people, 8.6% ± 2.7% vs 10.43% ± 3.5%; 20.95% ± 15.5% vs. 50.86% ± 4.2%, respectively… **We discussed the cause of declined immune function of lymphocytes of aged person and the mechanism of the effect of P. ginseng on lymphocytes."** *(Liu J, Wang S, Liu H, Yang L, Nan G. Stimulatory effect of saponin from Panax ginseng on immune function of lymphocytes in the elderly. Mech Ageing Dev 1995; 83: 43-53).*

72 "The immunopotentiating effects of the traditional Chinese drugs Ginsenoside (GS) and Glycyrrhiza polysaccharide (GPS) are reported. It was demonstrated that GS promotes the phagocytic activity of plaque-forming cells (PFC) and enhances the

espressione dei recettori per l'interleuchina 2 (IL-2) ed alla proliferazione delle cellule immunitarie della milza[73,74]. È noto che la depressione immunitaria che colpisce l'anziano è caratterizzata proprio da una ridotta capacità proliferativa dei linfociti e da una ridotta produzione di IL-2[75].

In *vivo* il *Panax ginseng* stimola l'attività delle cellule "natural killer" (NK) e ne facilita il recupero dell'attività, quando questa sia stata compromessa sperimentalmente. Inoltre, il *Panax ginseng* difende l'animale da esperimento dall'infezione sperimentale con *L. monocytogenes*. Sempre nel topo, alla dose di 10 mg/kg, il ginsenoside Rg1 aumenta il numero delle "plaque-forming cells" e delle agglutinine ematiche indotte dalla somministrazione di un antigene, e stimola l'attività delle cellule natural killer[76]. Il ginsenoside Rg1, inoltre, ripristina la funzionalità delle difese immunitarie, dopo che queste sono state compromesse da un trattamento con ciclofosfamide. L'attività immunostimolante del *Panax ginseng* è stata studiata nell'uomo in una sperimentazione clinica in doppio cieco. Gruppi di 20 volontari sani sono stati trattati per 8 settimane con placebo, estratto acquoso di Ginseng ed estratto standardizzato di ginseng, alla posologia di 100 mg x 2/die. In entrambi i gruppi trattati con Ginseng è stato osservato un aumento statisticamente significativo della chemotassi e dell'attività fagocitaria dei polimorfonucleati (PMN), dei linfociti totali e dei linfociti T4 (helper) e T8 (suppressor),

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mitogenesis of T and B lymphocytes primed by mitogens. **The mechanism of these effects is related to the ratio of cGMP to cAMP…**" *(Yang G, Yu Y. Immunopotentiating effect of traditional Chinese drugs: ginsenoside and glycyrrhiza polysaccharide. Proc Chin Acad Med Sci Peking Union Med Coll 1990; 5: 188-93).*

73 "Using methods of fluorescence flow cytometry and Western blot analysis, Rg1 was found to enhance the expression of IL-2 receptor α chain and inhibit the release of soluble IL-2 receptor… **the results of the present studies suggest that one of the mechanisms by which Rg1 enhances immune function in old rats might be mediated by increase of cAMP and cGMP contents**, resulting in IL-2 gene expression and splenocyteproliferation." *(Liu M, Zhang JT Studies on the mechanisms of immunoregulatory effects of ginsenoside Rg1 in aged rats. Yao Hsueh Hsueh Pao 1996; 31: 95-100).*

74 "Male BALB/c mice were treated orally for 30 consecutive days with 2 g/kg of a 50% ethanol extract of ginseng root. Mice treated with ginseng and immunized with ovalbumin (OVA), resulting in an eight-fold increase in titers of anti-OVA immunoglobulin (Ig)G in the serum compared to the group receiving OVA immunization without ginseng treatment; the level of IgG was also significantly elevated in the mice treated with ginseng and immunized with OVA. Mice treated with ginseng without OVA immunization exhibited significantly reduced IgG and IgA production by spleen cells. However, IgG production was not affected in mice treated with ginseng and OVA immunization in spleen cells. Interleukin (IL)-2, interferon (IFN)-gamma and IL-4 secretion by spleen cells from either ginseng-treated mice or OVA-immunized mice were down-regulated compared to that in the control group; while the production of IL-10 was unchanged. The percentage of CD8+ cells was significantly reduced in spleen cells from ginseng-treated, OVA-immunized mice. Thus, long-term oral administration of ginseng extract appears to potentiate humoral immune response but suppress spleen cell functions." *(Liou CJ, Huang WC, Tseng J. Long-term oral administration of ginseng extract modulates humoral immune response and spleen cell functions. Am J Chin Med. 2005; 33(4):651-61.)*

75 "In the present studies, **Rg1 was shown to selectively enhance the proliferation of lymphocytes and the production of IL-2 in aged rats**… According to these results, it is reasonable to consider Rg1 an immunoregulator rather than a purely "immunopotentiating agent." *(Liu M, Zhang JT. Immunoregulatory effects of ginsenoside Rg1 in aged rats. Yao Hsueh Hsueh Pao 1995; 30: 818-23).*

76 "*Panax ginseng*, employed for its putative medicinal properties in South Asia, was examined for its immunomodulatory properties in mice… Panax ginseng provided a degree of protection against infection with L. monocytes… **Taken together, these data suggest that Panax ginseng has some immunomodulatory properties, primarily associated with NK cell activity.**" *(Kim JY, Germolec DR, Luster MI. Immunotoxicology Group, Panax ginseng as a potential immunomodulator: studies in mice. Immunopharmacol Immunotoxicol 1990; 12:257-76).*

e dell'attività delle cellule NK. L'effetto immunostimolante era più marcato nei volontari trattati con l'estratto standardizzato, che con l'estratto acquoso[77].

All'attività immunostimolante del *Panax ginseng* potrebbero contribuire, oltre ai ginsenosidi, le saikosaponine[78], alcuni polipeptidi e due polisaccaridi isolati dalla radice – il ginsenano S-IA ed il ginsenano S-IIA – che hanno mostrato una attività protettiva del sistema reticoloendoteliale ed una attività anticomplementare[79]. Un altro polisaccaride – il ramnogalacturonano II (GL-4IIb2) – stimola nell'uomo l'attività dei macrofagi[80]. Un recente studio *in vivo* ha analizzato l'effetto degli estratti di Ginseng e Salvia in ratti infettati con virus dell'influenza, mostrando una maggiore efficacia nella produzione di anticorpi antinfluenzali rispetto al gruppo trattato con virus inattivato. Questi risultati permettono di ipotizzare che l'estratto di ginseng possa avere una funzione protettiva ed immunomodulante verso questa tipologia di virus[81].

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77 "The effect of Panax ginseng extracts on cell-mediated immune functions in man has been investigated. Three groups, each consisting of twenty healthy volunteers, were treated under conditions of double blindness with capsules containing lactose (Control Group B), with capsules containing 100 mg of aqueous extract of the drug (Group A), and with capsules containing 100 mg of standardized extract of the drug (Group C). All the patients took one capsule every 12 h for 8 weeks. Blood samples were withdrawn before beginning the treatment, at the fourth week and at the eighth week. The immune parameters examined were the following: chemotaxis of PMNs, phagocytosis index (PHI), phagocytosis fraction (PHF), intracellular killing, total lymphocytes (T3), T helper (T4) subset, suppressor cells (T8) subset, blastogenesis of circulating lymphocytes, natural killer-cell activity (NK). Chemotaxis proved to be enhanced ($p<0.05$) already at the fourth week in Group A as well as in Group C; the increase became even more marked ($p<0.001$) at the eight week in subjects belonging to Group C. PHI and PHF proved to be enhanced ($p<0.05$) at the eighth week in subjects of Group A; these increases were found to be higher in subjects of Group C ($p<0.001$) already starting at the fourth week. Intracellular killing was shown to be significantly increased ($p<0.05$) already at the fourth week in Groups A and C; the increase becomes highly significant in both groups ($p<0.001$) at the eighth week; however, a significant increase ($p<0.05$) at the eighth week was also noticed in the placebo group (Group B.)." *(Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer. Drugs Exp Clin Res 1990; 16: 537-42).*

78 "Macrophage activation by saikosaponins and saikogenins was investigated and compared with that by other saponins and macrophage stimulants. **Saikosaponins a and d induced a marked cell accumulation in the peritoneal cavity when administered intraperitoneally.**" *(Kumazawa Y, Takimoto H, Nishimura C, Kawakita T, Nomoto K. Activation of murine peritoneal macrophages by saikosaponin a, saikosaponin d and saikogenin d. Int J Immunopharmacol 1989;11: 21-8).*

79 "Two acidic polysaccharides, called ginsenan S-IA and ginsenan S-IIA, were isolated from the root of Panax ginseng C. A. Meyer… **Both polysaccharides showed remarkable reticuloendothelial system-potentiating activity in a carbon clearance test and pronounced anti-complementary activity**. These substances are the first examples having a relatively high content of both α-3,5-branched L-arabinose and β-1,4-linked D-galactose units among the acidic arabinogalactans with activities on phagocytosis and anti-complement." *(Tomoda M, Hirabayashi K, Shimizu N, Gonda R, Ohara N, Takada K Characterization of two novel polysaccharides having immunological activities from the root of Panax ginseng. Biol Pharm Bull 1993; 16: 1087-90).*

80 "A complex pectic polysaccharide (GL-4IIb2) has been isolated from the leaves of Panax ginseng C.A. Meyer, and shown to be a macrophage Fc receptor expression-enhancing polysaccharide." *(Shin KS, Kiyohara H, Matsumoto T, Yamada H. Rhamnogalacturonan II from the leaves of Panax ginseng C.A. Meyer as a macrophage Fc receptor expression-enhancing polysaccharide. Carbohydr Res 1997; 300: 239-49).*

81 "We have investigated the adjuvant roles of common herbal medicines (ginseng, Salviae) and their effects on early immune responses during influenza virus infection in a mouse model. Intranasal co-administration with inactivated influenza virus A (PR8) and ginseng or Salviae extract increased the levels of influenza virus specific antibodies and neutralizing activities compared to immunization with PR8 alone, and provided protective immunity. Salviae co-administration significantly enhanced IFN-gamma and IL-2 cytokine producing splenocytes while ginseng induced high levels of IL-4 and IL-5 cytokine producing cells after challenge infection. Cells expressing an early activation marker CD69 and levels of a pro-inflammatory cytokine IL-6 were highly elevated in lungs from naïve mice during challenge virus infection, which might be a mechanism in lung inflammation leading to death.

Sinergismo con i vaccini influenzali. Come conseguenza della sua attività stimolante la risposta immunitaria, il *Panax ginseng* sembra potenziare gli effetti protettivi del vaccino antinfluenzale in una sperimentazione clinica in doppio cieco controllata[82,83].

Attività anti-invecchiamento. Come conseguenza degli effetti sul sistema immunitario e sulla memoria, il *Panax ginseng* è proposto – da solo o in associazione ad altri fitocomplessi[84] – come un rimedio contro l'invecchiamento. In una sperimentazione clinica in singolo cieco, il *Panax ginseng* prolunga in qualche modo la funzionalità dell'organismo nell'anziano, gli AA. tuttavia non specificano i termini del miglioramento[85], anche se sembrano migliorati i parametri della qualità

In contrast, immunized mice that were co-administered ginseng or Salviae modulated CD69 expressing immune cells, did not produce IL-6, and showed significant enhancement of influenza virus specific IgA antibody in lungs after challenge virus infection. Therefore, these results indicate that both ginseng and Salviae play a role as mucosal adjuvants against influenza virus as well as immuno-modulators during influenza virus infection." *(Quan FS, Compans RW, Cho YK, Kang SM. Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine. 2007 Jan 4;25(2):272-82).*

82 "The aim of the study was to determine the properties of a standardized extract of ginseng root in inducing a higher immune response in vaccination against influenza. Attention was also paid to the common cold in this multicentre, two-arm, randomized, placebo-controlled, double-blind investigation. A total of 227 volunteers who visited 3 private practices in Milan received daily oral capsule doses of either placebo (113) or 100 mg of standardized ginseng extract G115 (114) for a period of 12 weeks… **As a result, while the frequency of influenza or common cold between weeks 4 and 12 was 42 cases in the placebo group, it was only 15 cases in the G115 group, the difference being statistically highly significant (p < 0.001)…** Natural killer (NK) activity levels at weeks 8 and 12 were nearly twice as high in the G115 group as compared to the placebo group (p < 0.0001). In all the volunteers, laboratory values of 24 safety parameters showed no significant differences between the end and the beginning of the 12-week study in either of the groups. There were only 9 adverse events in the study, the principal one being insomnia." *(Scaglione F, Cattaneo G, Alessandria M, Cogo R. Efficacy and safety of the standardised Ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold. Drugs Exp Clin Res 1996; 22: 65-72).*

83 "The dry extract prepared from the Panax ginseng C.A. Meyer-root (total ginseng (T-ginseng)) contain ginsenosides (G-des) which were shown to have adjuvant properties as demonstrated by: (a) injecting guinea pigs with a mixture of T-ginseng and inactivated porcine parvovirus (PPV) as a conventional vaccine; (b)injecting PPV-antigen and T-ginseng simultaneously but separately at different sites on the animal and (c)injecting only the T-ginseng 1 or 2 weeks prior to immunisation with the PPV-antigen….Immunisations using PPV-vaccines adjuvanted with single purified G-des demonstrated that the ginseng fractions Rb1 and Rg1 are potent adjuvants inducing higher or similar antibody titres than the vaccine adjuvanted with Al(OH)(3), e.g. Rb1 tested at a concentration of 830 microg per dose induced a significantly (P = 0.009) higher antibody titre than the one adjuvanted with Al(OH)(3)." *(Rivera E, Hu S, Concha C. Ginseng and aluminium hydroxide act synergistically as vaccine adjuvants. Vaccine. 2003 Mar 7; 21(11-12):1149-57.)*

84 "The development of a predominantly geriatric community worldwide has become an inevitable fact. Antiageing agents could be, in a certain sense, attentive to the well-being of the aged… A list of Chinese medicinal plants used as or related to the antiageing agents are presented. Specifically, five Chinese traditional drugs, Herba Epimedii, Fructus Lycii, Radix Polygoni multiflori, Radix Cynanchi auriculati and Ganoderma along with a composite prescription 'American Ginseng Royal Jelly' are selected as representatives. The prospect of research and development of antiageing drugs based on natural origin is also discussed." *(Xiao PG, Xing ST, Wang LW. Immunological aspects of Chinese medicinal plants as antiageing drugs. J Ethnopharmacol 1993; 38: 167-75).*

85 "…71 cases with age over sixty were randomly divided into treated group and control group, and observed by single-blind method. 36 cases were administered with American ginseng compound liquor as a treated group, 35 cases were administered with American ginseng liquor only as a control group… I**t showed that these two recipes both had the efficiency on prolonging the functional age (P<0.05).**" *(Cui J, Chen KJ. American ginseng compound liquor on retarding-aging process. Chung Hsi I Chieh Ho Tsa Chih 1991; 11: 457-60).*

di vita[86]. In un altro studio condotto su 358 pazienti di età media-avanzata, la somministrazione di saponine di *Panax ginseng* 50 mg x 3/die determina un effetto "anti-senilità", descritto dagli AA. come un effetto benefico sulla memoria, sulla funzionalità delle difese immunitarie e del corticosurrene, sull'attività cardiocircolatoria, con riduzione del numero di episodi di angina pectoris e di extrasistoli ventricolari[87]. Tuttavia, alcuni AA. non escludono un effetto diretto sul processo di invecchiamento[88], mentre altri negano un effetto del *Panax ginseng* nell'anziano[89]. È da notate che il malonil-ginsenoside Rb1 potenzia la crescita dei neuroni indotta da NGF (nerve growth factor), e questa attività potrebbe influire positivamente sulla perdita di cellule neuronali caratteristica dell'invecchiamento cerebrale[90].

Attività antiaggregante piastrinica. Il panaxinolo ed i ginsenosidi Ro, Rg1 ed Rg2, inibiscono l'aggregazione piastrinica, ma solo il panaxinolo riduce la formazione di trombossano in piastrine di coniglio[91]. Il panaxinolo agisce sull'aggregazione indotta da collagene, acido arachidonico, ADP, ionoforo A23187, PAF e trombina, inibendo la produzione di trombossano e bloccando la seconda

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86 *Coleman CI, Hebert JH, Reddy P. The effects of Panax ginseng on quality of life. J Clin Pharm Ther. 2003 Feb; 28(1):5-15.*

87 "The results showed that Ginseng-Rhizome saponin (GRS) possessed antisenility effect and marked effect on relieving the symptoms of aging, adjusting organic metabolism and improving physiological function, ecc., such as promoting memory, raising the amount of white cells and improving organic immunity function. GRS both improved the function of hypophysisgonad axis and the function of adrenal cortex." *(Zhao XZ. Antisenility effect of ginseng-rhizome saponin. Chung Hsi I Chieh Ho Tsa Chih 1990; 10:586-9, 579).*

88 "These results revealed that the ANP gene expression declined during ontogenic ageing development and **ginsenosides possessed anti-ageing effects in the heart endocrineous function aspect.**" *(Hong M, Jin Y, Mai YQ, Boersma A, Han KK, Vantyghem MC, Lefebvre J. The decline of atrial natriuretic peptide (ANP) gene expression in older rats and the effects of ginsenoside on ANP gene expression. Comp Biochem Physiol B 1992; 101: 35-9).*

89 "This study aimed to examine the effect of ginseng as an adjuvant to treatment and rehabilitation of geriatric patients in a double blind, controlled clinical trial… In conclusion, **no identifiable effect of ginseng as an adjuvant to treatment and rehabilitation of geriatric patients was observed.**" *(Thommessen B, Laake K. No identifiable effect of ginseng (Gericomplex) as an adjuvant in the treatment of geriatric patients. Aging 1996; 8: 417-20).*

90 "Effects of malonylginsenoside Rb1 (GRb1-m) isolated from dried root of Panax ginseng C. A. Meyer (Araliaceae) on neuronal survival and neurite outgrowth were compared with those of ginsenoside Rb1 (GRb1)… **These results suggest, first, that GRb1-m potentiates NGF-induced neurite outgrowth of chick embryonic DRGs and DRG neurons, but behaves in a slightly different manner from GRb1**, and, second, that the effects of the two saponins may work primarily on neurons causing the potentiation of NGF-induced neurite outgrowth." *(Nishiyama N, Cho SI, Kitagawa I, Saito H. Malonylginsenoside Rb1 potentiates nerve growth factor (NGF)-induced neurite outgrowth of cultured chick embryonic dorsal root ganglia. Biol Pharm Bull 1994; 17: 509-13).*

91 "Panaxynol and ginsenosides Ro, Rg1, and Rg2 were found to be the main antiplatelet components in the diethyl ether and 1-butanol fractions… **Panaxynol inhibited the aggregation, release reaction, and thromboxane formation in rabbit platelets while ginsenosides Ro, Rg1, and Rg2 suppressed the release reaction only.**" *(Kuo SC, Teng CM, Lee JC, Ko FN, Chen SC, Wu TS. Antiplatelet components in Panax ginseng. Planta Med 1990; 56: 164-7).*

fase della aggregazione[92]. Risultati analoghi sono stati osservati su piastrine umane[93]. *In vivo* la somministrazione di ginsenosidi a dosi comprese fra 25 e 100 mg/kg p.o. nel coniglio, stimola la produzione di prostaciclina e riduce quella di trombossano[94]. Un supplemento dietetico con *Panax ginseng* alla percentuale dello 0,0025% modifica la concentrazione intrapiastrinica dei nucleotidi ciclici, riducendo la potenzialità proaggregante delle piastrine[95].

Attività sull'apparato cardiovascolare. Il *Panax ginseng* ed i ginsenosidi risultano attivi in molti modelli di ischemia-riperfusione del cervello alla dose di 100 mg/kg iv[96], e nel miocardio alla dose di 100-200 mg/kg[97]. In un modello di ischemia-riperfusione del miocardio da legatura dell'arteria coronarica, i ginsenosidi sono risultati attivi nel ridurre i segni biochimici ed elettrofisiologici di ischemia alla dose di 10 mg/kg IV o con una infusione di 80 µg/kg/min[98]. In un modello sperimentale

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92 "The antiplatelet effect of panaxynol isolated from the diethyl ether layer was compared with those of ginsenosides… **It is concluded that panaxynol is the most potent antiplatelet agent in ginseng and its mechanism of action is chiefly due to the inhibition of thromboxane formation.**" *(Teng CM, Kuo SC, Ko FN, Lee JC, Lee LG, Chen SC, Huang TF. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. Biochim Biophys Acta 1989; 990: 315-20).*

93 "The non-saponin fraction (NSF; lipophilic fraction) from the roots of Panax ginseng inhibited the aggregation of human platelets induced by thrombin (0.1 units/ml) in a dose-dependent manner… **The results suggest that NSF may regulate the levels of cGMP and TXA2 to inhibit platelet aggregation induced by thrombin.**" *(Park HJ, Rhee MH, Park KM, Nam KY, Park KH. Effect of non-saponin fraction from Panax ginseng on cGMP and thromboxane A2 in human platelet aggregation. J Ethnopharmacol 1995; 49: 157-62).*

94 "Total saponins of Panax notoginseng (PNS) were given orally 100 mg/(kg.d) to rabbit for 8 wk… **These results show that the anti-atherosclerotic action of PNS may be a result of the correction of the unbalance between prostacyclin and thromboxane A_2.**" *(Shi L, Fan PS, Wu L, Fang JX, Han ZX. Effects of total saponins of Panax notoginseng on increasing PGI2 in carotid artery and decreasing TXA2 in blood platelets. Chung Kuo Yao Li Hsueh Pao 1990; 11: 29-32).*

95 "We have studied the effect of dietary supplementation with 25 mg (0.0025% of the total diet) of a lipophilic fraction (LF) from Panax ginseng on rat platelet aggregation induced by collagen or thrombin, and on blood coagulation… **these results suggest that dietary LF regulates the levels of cGMP and cAMP, and prolongs the time interval (TT, APTT) between the conversion of fibrinogen to fibrin**. Accordingly, our data demonstrate that dietary LF has an antithrombotic effect in vivo" *(Park HJ, Lee JH, Song YB, Park KH. Effects of dietary supplementation of lipophilic fraction from Panax ginseng on cGMP and cAMP in rat platelets and on blood coagulation. Biol Pharm Bull 1996; 19: 1434-9).*

96 "The correlation between protective effect of ginsenosides Rb + R0 and brain endogenously-derived prostacyclin synthesis, thromboxane A2 formation and lipid peroxidation were estimated in rats… **It is concluded that ginsenosides possess protective effect on cerebral ischemia-reperfusion injury of rats and ginsenosides Rb + R0 are the active principles.** The underlying mechanism of protection is ascribed partially or mainly to the facilitated synthesis and release of prostacyclin, reduced formation of thromboxane A2 and inhibited generation of free radicals and subsequent lipid peroxidation." *(Chu GX, Chen X. Anti-lipid peroxidation and protection of ginsenosides against cerebral ischemia-reperfusion injuries in rats. Chung Kuo Yao Li Hsueh Pao 1990; 11:119-23).*

97 "Effects of total saponins of Panax notoginseng (PNS) and purified ginsenosides Rb1 and Rg1 from PNS on myocardial injury induced by cardiac ischemia and reperfusion were studied with rat hearts in situ and in vitro… **The results show that PNS, Rb1, and Rg1 prevent cardiac ischemia and the action is considered to be related to the inhibition of lipid peroxidation.**" *(Li X, Chen JX, Sun JJ. Protective effects of Panax notoginseng saponins on experimental myocardial injury induced by ischemia and reperfusion in rat. Chung Kuo Yao Li Hsueh Pao 1990; 11: 26-9).*

98 "To verify whether ginsenosides will attenuate the myocardial ischemia and reperfusion injury, the left anterior descending coronary artery (LAD) was snared for 2 hours in 23 dogs and then the ischemic myocardium was reperfused. 45 minutes after ischemia, the animals were randomly divided into a ginsenosides group (n = 11, receiving a slow IV bolus of ginsenosides 10

di infarto del miocardio, i ginsenosidi sono risultati attivi alla posologia di 100 mg/kg i.p[99]. L'effetto protettivo del *Panax ginseng* si estende anche ai danni da ischemia del rene, dove i ginsenosidi alla dose di 30 mg/kg migliorano la funzionalità renale compromessa da una condizione ischemica sperimentale[100].

All'attività protettiva nei confronti dell'apparato cardiovascolare contribuisce in larga misura l'effetto stimolatorio del *Panax ginseng* sulla produzione di ossido nitrico ad attività vasodilatatrice. In associazione a *Ligusticum chuanxiong Hort., Carthamus tinctorius L.* e *Salvia miltiorrhiza Bge, il Panax ginseng* è risultato altrettanto attivo della nifedipina nel ridurre il danno neuronale conseguente ad una ischemia parziale del sistema nervoso centrale da legatura delle carotidi nel ratto[101]. Associato all'*Astragalus mongholicus* e alla *Angelica sinensis*, il *Panax ginseng* è stato utilizzato nel prevenire l'ipertensione polmonare e la ridotta contrattilità ventricolare sinistra conseguenti ad ipossia polmonare, indotta nel ratto in una camera ipobarica che riproduceva le condizioni atmosferiche di una altezza di 5000 m circa. Il prodotto "Qi-Xue" si è dimostrato efficace nel migliorare la contrattilità miocardica e nel ridurre l'aumento della pressione polmonare[102].

In vivo il *Panax ginseng* protegge il coniglio dalle alterazioni del seno nodale alla dose di 50 mg/kg[103]. Nell'uomo, la somministrazione di 200 mg di *Panax ginseng* in associazione al *Ginkgo biloba*, determina una riduzione della pressione arteriosa, della frequenza cardiaca e della aggregazione piastrinica[104]. Una sperimentazione clinica randomizzata ha dimostrato l'efficacia dei ginsenosidi

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mg/kg and then a continuous infusion of 80 µg/kg/min) and a saline solution group (n = 12 receiving equal amount of glucose in saline)… **These results show that ginsenosides can protect the ischemic myocardium and reperfusion injury of myocardium.**" *(Zhang J, Sun JP, He JB. Protective effects of ginsenosides in myocardial ischemia and reperfusion injury. Chung Hua Nei Ko Tsa Chih 1990; 29: 653-5).*

99 "In the model of myocardial infarction produced by occlusion of left anterior descending coronary artery (LAD) in rabbit, gypenosides (GP 100 but not 50 mg/kg, ip) reduced myocardial infarct size and decreased serum free fatty acid (FFA)… **The results indicate that the protective effect of GP on myocardial infarction may be correlated with its prevention of myocardial lipid peroxidation, and attributed to the amelioration of FFA metabolic deterioration."** *(Xiong WS, Yan XD, Shen N, Qiu FL, Chen X. Protective effects of gypenosides on experimental myocardial infarction. Chung Kuo Yao Li Hsueh Pao 1990; 11: 427-30).*

100 *Zhang Y. Protective effects of ginsenosides on warm ischemic damages of the rabbit kidney. Chung Hua I Hsueh Tsa Chih 1992; 72:84-5.*

101 *Leung AW, Mo ZX, Zheng YS. N.T. Reduction of cellular damage induced by cerebral ischemia in rats. Neurochem Res 1991; 16: 687-92).*

102 *Zhao L. Prevention of hypoxic pulmonary hypertension with "qi-xue" injection. Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao 1990; 12: 51-5.*

103 "This experiment was carried out to evaluate the effect of ginsenosides from stems and leaves (GSL) on the sinus node dysfunction (SND) by observing the changes of the electrophysiological parameters of sinus node in limited period… **It was suggested that GSL exerted protective effects on the experimental sinus node dysfunction.**" *(Gao D, Lou F, Jin F. Protection on experimental sinus node dysfunction in rabbits with ginsenosides. Chung Hua Hsin Hsueh Kuan Ping Tsa Chih 1992; 20: 38-40).*

104 "Gincosan is a combined preparation containing 60 mg ginkgo biloba and 100 mg ginseng, standardized of 24% ginkgo flavone glycosides and 4% ginsenosides. Hemorrheological and circulatory effect as well as blood pressure behavior after the administration of gincosan were studied in an acute trial on 10 voluntary subjects… **Diastolic blood pressure and heart rate decreased only in the high dosage group. The pathologically increased spontaneous platelet aggregation is reduced by both dosages…** A trend towards a decrease in the systolic blood pressure is revealed ($p<0.1$)." *(Kiesewetter H, Jung F, Mrowietz C, Wenzel E. Int J Clin Pharmacol Ther Toxicol 1992; 30: 97-102).*

nella prevenzione dei danni da ischemia miocardica durante interventi chirurgici a cielo aperto[105]. Analoghi risultati sono stati ottenuti con il *Panax ginseng* in associazione con *Radix Paeoniae alba*[106]. Lo stesso composto è stato utilizzato in soggetti con cardiopatia ischemica, nei quali ha ridotto l'incidenza di angina pectoris di oltre il 90% e le alterazioni ischemiche dell'ECG, ed ha migliorato le capacità fisiche al "Treadmill test"[107]. L'effetto sembra dovuto ad una attività cronotropa e batmotropa negativa, dimostrato anche *in vitro* da una riduzione del potenziale di azione e dell'eccitabilità di cardiomiociti di ratto[108]. Il Ginseng e più precisamente i ginsenosidi possiedono un'attività angiomodulatoria[109]. Gli effetti del *Panax ginseng* sul sistema cardiovascolare sembrano estendersi anche ad una attività protettiva nei confronti dello sviluppo dell'aterosclerosi. Infatti, il *Panax ginseng* inibisce la migrazione di fibrocellule muscolari lisce nell'intima delle arterie, uno dei primi stadi della formazione della placca aterosclerotica[110].

Attività ipoglicemizzante. Il ginsenoside Rg1 possiede una efficace azione ipoglicemizzante: l'effetto è dose-dipendente, dura circa 4 ore e non si riduce con la somministrazione ripetuta. Il meccanismo dell'attività ipoglicemizzante dei ginsenosidi non è noto. La liberazione di insulina da cellule di ratto in vitro in risposta ad elevate concentrazioni di glucosio risulta potenziata in presenza di un estratto di *Panax ginseng*[111]. Il ginsenoside Rg1 non interferisce, né positivamente né negativamente, con

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105 "Thirty mitral valvular surgical patients were randomly divided into three groups for study of protective effects of Ginsenoside on myocardiac ischemic and reperfusion injuries… **We conclude that both Ginsenoside in total and Ginsenoside Rb have protective effects on myocardiac ischemic and reperfusion injuries in open heart surgery, and the effect of Ginsenoside in total is even better than that of Ginsenoside Rb.**" *(Zhan Y, Xu XH, Jiang YP. Protective effects of ginsenoside on myocardiac ischemic and reperfusion injuries. Chung Hua I Hsueh Tsa Chih 1994; 74: 626-8).*

106 *Hu JX, Jia GX, Yan ZR. General Hospital of Air Force, PLA of China, Beijing. Clinical and experimental study of shenshao tongguan pian in treating angina pectoris of coronary heart disease. Chung Hsi I Chieh Ho Tsa Chih 1990; 10: 596-9.*

107 *Liao JZ, Chen JJ, Wu ZM, Guo WQ, Zhao LY, Qin LM, Wang SR, Zhao YR. Clinical and experimental studies of coronary heart disease treated with yi-qi huo-xue injection. J Tradit Chin Med 1989; 9: 193-8.*

108 *Jiang Y, Zhong GG, Chen L, Ma XY. Influences of ginsenosides Rb1, Rb2, and Rb3 on electric and contractile activities of normal and damaged cultured myocardiocytes. Chung Kuo Yao Li Hsueh Pao 1992; 13: 403-6.*

109 *Leung KW, Yung KK, Mak NK, Yue PY, Luo HB, Cheng YK, Fan TP, Yeung HW, Ng TB, Wong RN. Angiomodulatory and neurological effects of ginsenosides. Curr Med Chem. 2007; 14(12):1371-80.*

110 "Migration of arterial smooth muscle cells (SMC) in the arterial wall plays an important role in the formation of intimal thickening of atherosclerotic lesions. In this study, we examined the effect of ginsenosides on SMC migration induced by platelet-derived growth factor (PDGF) and SMC-derived migration factor (SDMF). **Ginsenosides had inhibitory effects on SMC migration and the striking effects were observed with ginsenoside-Rb2 and -Rc in a dose-dependent manner. These results suggest that the administration of ginsenosides on the patients may prevent intimal thickening, in part, by inhibiting SMC migration in the arterial wal.**" *(Koyama N, Morisaki N, Saito Y, Yoshida SInhibitory effect of ginsenosides on migration of arterial smooth muscle cells. Am J Chin Med 1992; 20: 167-73).*

111 "We investigated the long-term (24h) influence of high concentration glucose (26.4 mmol/L) on insulin release by culturing collagenase isolated rat pancreatic islets in vitro… **When added to the culture medium with 26.4 mmol/L glucose, Ginseng saponins markedly increased the responsiveness of islets to glucose stimulation, and augmented the sensitivity of incubated islets to additional Ginseng saponins.**" *(Li Q. Effect of hyperglycemia on insulin release from isolated rat pancreatic islets. Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao 1993; 15: 187-92).*

l'azione dell'insulina, e le concentrazioni intracellulari di cAMP nell'epatocita non sono modificate dalla somministrazione di ginsenoside; al contrario, il trasporto intraepatocitario di glucosio è fortemente aumentato in presenza di ginsenoside[112]. Questo suggerisce che il ginsenoside aumenti l'espressione sulla membrana cellulare dell'epatocita delle proteine trasportatrici di glucosio. Alcune evidenze sperimentali sembrano suggerire un aumento della quantità di GLUT2 sulla superficie dell'epatocita[113]. Alcuni AA. hanno descritto attività insulino-simili del *Panax ginseng*, quali l'inibizione della lipolisi indotta da adrenalina e la stimolazione della lipogenesi a partire dal glucosio. Gli stessi AA. hanno identificato nell'acido piroglutammico il componente responsabile di queste azioni[114]. Anche alcuni polipeptidi del *Panax ginseng* avrebbero una attività ipoglicemizzante dopo somministrazione parenterale di 50-200 mg/kg, sia nell'animale normale sia nell'animale reso sperimentalmente diabetico. Questi polipeptidi sarebbero privi di attività sul metabolismo dei lipidi, e ridurrebbero la glicogenosintesi epatica. L'attività ipoglicemizzante ed inibente la glicogenosintesi epatica dei polipeptidi del *Panax ginseng*, sono antagonizzate da un pretrattamento, ripetitivamente, con fentolamina e propanololo, suggerendo che questi composti possano agire attraverso recettori adrenergici[115].

All'attività ipoglicemizzante del *Panax ginseng* potrebbero contribuire anche alcuni polisaccaridi (GH1) che, somministrati alla dose di 50-200 mg/kg ip o sc, ridurrebbero la glicemia e la gluconeogenesi. Gli stessi polisaccaridi, inoltre, stimolerebbero la fosforilazione ossidativa del glucosio, e l'attività di due enzimi – la succinato deidrogenasi e la citocromo ossidasi – aumentando l'utilizzazione

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[112] "Sanchinoside C1 (ginsenoside Rg1), one of the major effective components of Panax notoginseng, was reported to be effective in lowering glucose-induced hyperglycemia and synergizing the action of insulin in normal animals… **The results showed that sanchinoside C1 was able to lower plasma glucose level in alloxan-diabetic mice**. The action was strengthened with repeated administration and tended to be dose-dependent; its effect lasted for more than four hours and no synergism or antagonism between sanchinoside C1 and insulin was observed." *(Gong YH, Jiang JX, Li Z, Zhu LH, Zhang ZZ. Hypoglycemic effect of sanchinoside C1 in alloxan-diabetic mice. Yao Hsueh Hsueh Pao 1991; 26: 81-5).*

[113] "The oral administration of the water extract of Ginseng Radix (GR) to normal and epinephrine-induced hyperglycemic mice caused a significant decrease in the blood glucose level 4 h after its administration… **These results suggest that the hypoglycemic activity of GR is presumably due, at least in part, to the increment of GLUT2 protein content.**" *(Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E, Yano H, Tanigawa K, Seino Y. Effect of ginseng radix on GLUT2 protein content in mouse liver in normal and epinephrine-induced hyperglycemic mice. Biol Pharm Bull 1996; 19: 1238-40).*

[114] "Korean red ginseng powder was found to contain adenosine and an acidic substance which inhibited epinephrine-induced lipolysis and stimulated insulin-mediated lipogenesis from glucose (3, 4)… **Pyroglutamic acid exhibits selective modulations toward the opposite metabolic pathways in rat adipocytes; it inhibits the lipolysis but rather stimulates the lipogenesis.** Based on these results, we suggest to call these substances (adenosine and pyro-glutamic acid) "selective modulators." *(Takaku T, Kameda K, Matsuura Y, Sekiya K, Okuda H. Studies on insulin-like substances in Korean red ginseng. Planta Med 1990; 56: 27-30).*

[115] "When ginseng polypeptide (GP) was administered iv or sc to mice or rats, the blood sugar and liver glycogen were decreased… **The results suggest that the effect of GP on glucose metabolism may be related to adrenergic receptors. In addition, GP at doses which cause decreases of blood sugar and glycogen, inhibited LDH activity, and consequently produced decrease of lactic acid and increase of pyruvic acid.**" *(Wang BX, Yang M, Jin YL, Liu P. Studies on the mechanism of ginseng polypeptide induced hypoglycemia. Yao Hsueh Hsueh Pao 1990; 25: 727-31).*

dei glucidi e, conseguentemente, anche dei lipidi[116]. Al contrario dei ginsenosidi, il polisaccaride GH1 aumenta la concentrazione intraepatocitaria di cAMP, stimolando l'adenilato ciclasi (AC) ed inibendo l'attività delle fosfodiesterasi. Attraverso questi meccanismi, il polisaccaride GH1 promuove la glicogenolisi ed inibisce la gliconeogenesi[117]. L'efficacia terapeutica del *Panax ginseng* in soggetti con diabete mellito tipo II è stata studiata in una sperimentazione clinica in doppio cieco. I pazienti sono stati trattati con placebo o *Panax ginseng*, alla posologia di 100-200 mg/die, per 8 settimane. Al termine del trattamento è stata osservata una riduzione dell'emoglobina glicosilata (indice del controllo diabetico) ed una aumentata liberazione di insulina. Gli AA. suggeriscono pertanto l'uso del *Panax ginseng* nel trattamento coadiuvante del diabete[118]. Il ginsenoside Rg3 sembra favorire la riduzione del glucosio nel plasma aumentando la secrezione dell'insulina attraverso il coinvolgimento dei canali del potassio ATP sensibili[119]. Un interessante articolo mostra gli effetti antiiperglicemici e anti-obesità di *P. ginseng* e del suo componente principale, il ginsenoside Re in topi obesi. il trattamento con Ginseng porta ad una riduzione del livello di glucosio, di colesterolo e trigliceridi nel sangue e ad una diminuzione del peso corporeo associato ad aumento della spesa energetica e della temperatura corporea[120]. In seguito sono stati analizzati gli estratti di radici e frutti

116 "Ginseng polysaccharides (GH1) 50-200 mg/kg ip or sc reduced blood glucose and liver glycogen of mice…GH1 increased the content of pyruvic acid, but decreased the content of lactic acid by weakening the activity of lactate dehydrogenase. GH1 accelerated oxidative-phosphorylation of carbohydrate since the activities of succinate dehydrogenase (SDH) and cytochrome oxidase (CCO) were obviously stimulated… **It is suggested that the reduction of blood glucose and liver glycogen induced by GH1 be primarily due to the increase of carbohydrate utilization and the decrease of glycogenesis.**" *(Yang M, Wang BX, Jin YL, Wang Y, Cui ZY. Effects of ginseng polysaccharides on reducing blood glucose and liver glycogen. Chung Kuo Yao Li Hsueh Pao 1990; 11: 520-4).*

117 "The ginseng polysaccharides GH1 (100, 200 mg.kg-1) iv reduced liver glycogen and increased adenosine-3',5'-cyclic monophosphate (cAMP) level and adenyl cyclase (AC) activity in mice… **It is suggested that the reduction of liver glycogen induced by GH1 resulted from its obvious increase of cAMP which promoted glycogenolysis and decreased glycogenesis.**" *(Yang M, Wang BX. Effects of the ginseng polysaccharides on reducing liver glycogen. Chung Kuo Yao Li Hsueh Pao 1991; 12: 272-5).*

118 "To investigate the effect of ginseng on newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM) patients… In this double-blind placebo-controlled study, 36 NIDDM patients were treated for 8 weeks with ginseng (100 or 200 mg) or placebo. Efficacy was evaluated with psychophysical tests and measurements of glucose balance, serum lipids, aminoterminalpropeptide (PIIINP) concentration, and body weight… **Ginseng may be a useful therapeutic adjunct in the management of NIDDM.**" *(Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. Diabetes Care 1995; 18: 1373-5).*

119 *Park MW, Ha J, Chung SH. 20(S)-ginsenoside Rg3 enhances glucose-stimulated insulin secretion and activates AMPK. Biol Pharm Bull. 2008 Apr; 31(4):748-51.*

120 "Diabetes mellitus is characterized by hyperglycemia and complications affecting the eye, kidney, nerve and blood vessel. We have previously demonstrated the occurrence of oxidative stress of streptozotocin-induced diabetic rats, preceded by a depletion in the tissue level of glutathione. In this study, when diabetic rats were treated with ginsenoside Re of Panax ginseng C.A. Meyer, there was a significant reduction in blood glucose, total cholesterol and triglyceride levels. On the other hand, oxidative stress has been implicated in the pathogenesis of diabetes and its complications. It was found that treatment by ginsenoside Re restored the levels of both glutathione and malondialdehyde in the eye and kidney to those found in the control rats. This is the first report demonstrating ginsenoside Re has significant antioxidant efficacy in diabetes, and prevents the onset of oxidative stress in some vascular tissues. Our results demonstrated that ginsenoside Re could lower blood glucose and lipid levels, and exerts protective actions against the occurrence of oxidative stress in the eye and kidney of diabetic rats. Our data also provide evidence that ginsenoside Re could be used as an effective antidiabetic agent particularly in the prevention of diabetic microvasculopathy." *(Cho WC, Chung WS, Lee SK, Leung AW, Cheng CH, Yue KK. Ginsenoside Re of Panax ginseng possesses significant*

in un modello sperimentale di topo ob/ob (modello molto utilizzato per lo studio del diabete) per confrontare la differenza nella funzione ipoglicemizzante ed è stato visto che soltanto il frutto è in grado di ridurre la massa corporea e possiede un maggior potere antiiperglicemico[121]. Una recente pubblicazione indica che anche il malonylginsenoside (MGR) estratto dalla radice del *Panax ginseng* mostra un'attività antidiabetica in un modello murino di diabete indotto da streptozotocina[122].

Attività antigastrite e antiulcera. L'estratto di *Panax ginseng* previene la formazione di lesioni o ulcere gastriche, indotte con diverse metodiche[123]. Sono state estratte due frazioni polisaccaridiche di *Panax ginseng*, denominate GL-2 e GL-4, che risultano avere una buona attività preventiva sulla formazione di ulcere nel ratto da stress e da legatura del piloro[124]. Il polisaccaride GL-4 risulta attivo ad una posologia di 50-200 mg/kg per via sottocutanea[125]. Anche il polisaccaride GL-BIII risulta attivo come antiulcera[126]. L'attività antiulcera del Ginseng sembra dovuta ad una ridotta secrezione di acido cloridrico. Infatti, il *Panax ginseng* riduce la produzione di acido cloridrico, sia spontanea sia indotta da istamina e pentagastrina[127].

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antioxidant and antihyperlipidemic efficacies in streptozotocin-induced diabetic rats. Eur J Pharmacol. 2006 Nov 21; 550(1-3):173-9.)

121 "Previous studies demonstrated that both ginseng root and ginseng berry possess anti-diabetic activity. However, a direct comparison between the root and the berry under the same experimental conditions has not been conducted. In the present study, we compared anti-hyperglycemic effect between Panax ginseng root and Panax ginseng berry in ob/ob mice, which exhibit profound obesity and hyperglycemia that phenotypically resemble human type-2 diabetes. We observed that ob/ob mice had high baseline glucose levels (195 mg/dl). Ginseng root extract (150 mg/kg body wt.) and ginseng berry extract (150 mg/kg body wt.) significantly decreased fasting blood glucose to 143 +/- 9.3 mg/dl and 150 +/- 9.5 mg/dl on day 5, respectively (both $P < 0.01$ compared with the vehicle). On day 12, although fasting blood glucose level did not continue to decrease in the root group (155 +/- 12.7 mg/dl), the berry group became normoglycemic (129 +/- 7.3 mg/dl; $P < 0.01$). We further evaluated glucose tolerance using the intraperitoneal glucose tolerance test. On day 0, basal hyperglycemia was exacerbated by intraperitoneal glucose load, and failed to return to baseline after 120 min. After 12 days of treatment with ginseng root extract (150 mg/kg body wt.), the area under the curve (AUC) showed some decrease (9.6%). However, after 12 days of treatment with ginseng berry extract (150 mg/kg body wt.), overall glucose exposure improved significantly, and the AUC decreased 31.0% ($P < 0.01$). In addition, we observed that body weight did not change significantly after ginseng root extract (150 mg/kg body wt.) treatment, but the same concentration of ginseng berry extract significantly decreased body weight ($P < 0.01$). These data suggest that, compared to ginseng root, ginseng berry exhibits more potent anti-hyperglycemic activity, and only ginseng berry shows marked anti-obesity effects in ob/ob mice." *(Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. Anti-hyperglycemic effects of ginseng: comparison between root and berry. Phytomedicine. 2003; 10(6-7):600-5.)*

122 *Liu Z, Wang LJ, Li X, Hu JN, Chen Y, Ruan CC, Sun GZ. Hypoglycemic effects of malonyl-ginsenosides extracted from roots of Panax ginseng on streptozotocin-induced diabetic mice. Phytother Res. 2009 Oct; 23(10):1426-30.*

123 *Sun XB, Matsumoto T, Kiyohara H, Hirano M, Yamada H. Cytoprotective activity of pectic polysaccharides from the root of panax ginseng. J Ethnopharmacol 1991; 31: 101-7.*

124 *Sun XB, Matsumoto T, Yamada H. Purification of an anti-ulcer polysaccharide from the leaves of Panax ginseng. Planta Med 1992; 58: 445-8.*

125 *Sun XB, Matsumoto T, Yamada H. Anti-ulcer activity and mode of action of the polysaccharide fraction from the leaves of Panax ginseng. Planta Med1992; 58: 432-5.*

126 *Kiyohara H, Hirano M, Wen XG, Matsumoto T, Sun XB, Yamada H. Characterisation of an anti-ulcer pectic polysaccharide from leaves of Panax ginseng C.A. Meyer. Carbohydr Res 1994; 263: 89-101.*

127 *Suzuki Y, Ito Y, Konno C, Furuya T. Effects of tissue cultured ginseng on gastric secretion and pepsin activity. Yakugaku Zasshi.1991; 111: 770-4.*

Attività antiossidante. Come altri fitocomplessi, anche il *Panax ginseng* esercita una attività antiossidante[128], specialmente nei confronti della ossidazione da radicali liberi. Entrambi in ginsenosidi Rb1 ed Rg1 hanno una attività inibente la lipoperossidazione[129], come pure le saponine estratte dal *Panax ginseng*[130]. Impotenza maschile. È riportata una attività anti-impotenza maschile del *Panax ginseng* in soggetti con disfunzione erettile[131]. L'effetto potrebbe essere dovuto ad una aumentata produzione di ossido nitrico a livello dei corpi cavernosi[132]. In uno studio *in vivo* è stato somministrato per una settimana un estratto di ginseng sotto forma di 10 mg/ml nell'acqua da bere (corrispondente a 1,6 g/kg/die); un gruppo è stato quindi esposto ad ossigeno iperbarico (HBO) per 6 ore; due gruppi hanno bevuto solo l'acqua senza estratto e un dei due è stato esposto ad HBO. Cuori isolati di ratto, sottoposti a perfusione, sono stati sottoposti a lieve ischemia e quindi a riperfusione. I risultati hanno indicato che l'estratto di ginseng è stato in grado di prevenire il danno miocardico da ischemia/riperfusione e la compromissione della funzionalità endoteliale, mediante un'azione antiossidante[133].

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128 "This study was conducted to investigate whether or not the antioxidation effect of ginseng extract directly inhibits decomposition of unsaturated fatty acid caused by iron and hydrogen peroxide-induced lipid peroxidation, and whether this effect involves a hydroxyl radical-scavenging mechanism… **This antioxidant effect of ginseng may be responsible for its wide pharmacological actions in clinical practice by a free radical reaction-inhibition mechanism.**" *(Zhang D, Yasuda T, Yu Y, Zheng P, Kawabata T, Ma Y, Okada S. Ginseng extract scavenges hydroxyl radical and protects unsaturated fatty acids from decomposition caused by iron-mediated lipid peroxidation. Free Radic Biol Med 1996; 20: 145-50.*

129 "Ginsenosides Rb1 and Rg1 were found to inhibit to some degree both VitC-NADPH and Fe2(+)-cysteine induced lipid peroxidation of rat liver and brain microsomes… **The inhibitory effect of Rb1 on VitC-NADPH induced lipid peroxidation was similar to that of VitE at the same concentration.**" *(Huang YS. Effect of ginsenosides Rb1 and Rg1 on lipid peroxidation of rat in vitro. Chung Kuo I Hsueh Ko Hsueh Yuan Hsueh Pao 1989; 11: 460-2).*

130 *Sun WJ, Ma N, Ma LX, Zhang YL, Feng WL. The effect of ginseng stem, leaf and rhizoma saponins on the formation of lipid peroxides in rats of various ages. Chung Kuo Chung Yao Tsa Chih 1989; 14: 300-2.*

131 "To investigate the efficacy in treating erectile dysfunction and to develop a natural drug without complications, the results of ginseng treatments are compared to placebo and other drug. A total of 90 patients with 30 patients in each group were closely followed… **The overall therapeutic efficacies on erectile dysfunction were 60% for ginseng group and 30% for placebo and trazodone treated groups, statistically confirming the effect of ginseng ($p < 0.05$)…** The effects of saponin, extracted from ginseng, on smooth muscle of erectile tissues, can be evaluated using organ chamber or nitric oxide titration, thereby pinpointing the exact action mechanism of saponin. **As more informations are available, possible breakthrough in treatment of erectile dysfunction could be arisen from active saponin extracted from red ginseng, bringing hopes to many sufferers of erectile dysfunction.**" *(Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. Int J Impot Res 1995; 7: 181-6).*

132 "Ginsenosides, the active ingredients extracted from Panax ginseng, have been shown to promote nitric oxide (NO) release in bovine aortic endothelial cells… It is concluded that ginsenosides may release NO from endothelial cells, and enhance NO release from endothelial cells elicited by other vasoactive substances and from perivascular nitrergic nerves in the corpus cavernosum. **These endothelial and neurogenic effects of ginsenosides in inducing relaxation of the corpus cavernosum may account for the aphrodisiac effect of Panax ginseng.**" *(Chen X, Lee TJ. Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. Br J Pharmacol 1995; 115: 15-8).*

133 *Maffei Facino R, Carini M, Aldini G, Berti F, Rossoni G. Panax ginseng administration in the rat prevents myocardial ischemia-reperfusion damage induced by hyperbaric oxygen: evidence for an antioxidant intervention. Planta Med 1999; 65:614-9.*

Tollerabilità. Gli effetti collaterali riportati in letteratura sull'uso del Ginseng riguardano agitazione e/o insonnia dovute a dosi eccessive, somministrazioni serali o ipersensibilità individuale verso il prodotto. È stata descritta una sindrome da abuso di Ginseng caratterizzata da tachicardia, insonnia, diarrea e nervosismo, più evidente a seguito di dosi elevate di droga e se associata ad altri stimolanti del sistema nervoso centrale. Due casi di midriasi e difficoltà all'accomodazione sono stati osservati in pazienti che facevano uso di *Panax ginseng*[134]. Altri effetti collaterali sono stati osservati, generalmente riferibili ad un'attività anticolinergica[135]. l'assunzione di Ginseng sembra ridurre lievemente i livelli di glucosio nel sangue, tale effetto dovrebbe essere preso in considerazione in caso di associazione con antidiabetici orali, l'effetto potrebbe essere potenziato, anche se non esistono studi in merito. Inoltre è stato segnalato un caso di possibile interazione con warfarina, il meccanismo non è noto e sembra essere più associato al Ginseng Americano (*Panax quinquefolium*)[136,137,138,]. È sconsigliato l'uso del Ginseng in soggetti con ipertensione grave[139] ed in pazienti con patologie cardiache in terapia con cardiotonici[140]. Si sconsiglia l'uso nei bambini al di sotto dei 12 anni di età. Si consiglia di non assumere Ginseng in modo continuativo, ma effettuando cicli periodici intervallati da una sospensione temporanea del trattamento. Dalle informazioni trovate nelle monografie ufficiali del Ginseng si evince che gli effetti collaterali sono alquanto rari e le conclusioni riportate sono che l'uso del Ginseng non è associato a gravi effetti avversi se assunto ai dosaggi raccomandati. Tuttavia sono stati segnalati casi di effetti collaterali di tipo estrogenico in donne, sia nel periodo pre- che postmenopausa, che avevano utilizzato Ginseng. Mentre, in studi clinici su oltre 100 pazienti, ai quali è stato somministrato un estratto standardizzato di Ginseng, non sono stati osservati effetti collaterali di tipo estrogenico, e, in test specifici eseguiti in tali studi, sono stati riscontrati esclusivamente livelli ormonali normali nel sangue[141,142].

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134 *Lou BY, Li CF, Li PY, Ruan JP. Eye symptoms due to ginseng poisoning. Yen Ko Hsueh Pao 1989; 5: 96-7.*

135 *Chan TY. Anticholinergic poisoning due to Chinese herbal medicines. Vet Hum Toxicol 1995; 37: 156-7.*

136 *Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2004 May; 57(5):592-9.*

137 *Stockley's Herbal medicines Interactions. Pharmaceutical Press. 2009.*

138 *ESCOP Monographs. Ginseng radix. The Scientific Foundation for Herbal Medicinal Products. 2nd edition, Thieme, 2003*

139 *Adverse Effects of Herbal Drugs. Vol. II. De Smet PAGM, Keller K, Hänsel R, Chandler RF (eds), Springer-Verlag, Berlin, 1992, pag. 162-163.*

140 *Barnes J. Anderson L.A. Phillipson J.D. Ginseng, Panax. Herbal Medicines. third ed. Pharmaceutical Press 2007:325-336.*

141 *Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. Drug Saf. 2002; 25(5):323-44.*

142 *Mills S & Bone K. The essential guide to herbal safety. Ed. Elsevier.2005*