Iperico

Hypericum perforatum

Nome botanico

Hypericum perforatum L. *(Guttiferae)*

Parti usate

Sommità fiorite.

Componenti principali

Ipericina e pseudoipericina. Iperforine. Flavonoli glicosidi, biflavoni, tannini condensati e proantocianidine oligomeriche, xantoni.

Attività farmacologica

Attività antidepressiva e riequilibrante del tono dell'umore. Attività ansiolitica.

Impiego clinico

Stati depressivi da lievi a moderati.

Controindicazioni

Fotosensibilità nota. Per la mancanza di dati clinici l'Iperico non deve essere utilizzato nei bambini, in donne in gravidanza e durante l'allattamento.

Avvertenze e speciali precauzioni d'uso

Durante la terapia con *Hypericum perforatum* si dovrebbe evitare la prolungata esposizione alla luce diretta solare o a lampade abbronzanti. Non sono disponibili dati di sicurezza in pazienti con insufficienza renale o epatica; in questi pazienti la droga va pertanto usata con cautela.

Interazioni

Le sostanze presenti nelle preparazioni a base di iperico causano induzione di diversi enzimi responsabili del metabolismo dei farmaci. Ciò può portare a ridotti livelli plasmatici e a minore efficacia dei medicinali assunti contemporaneamente. In particolare, si sconsiglia l'uso concomitante con indinavir e altri farmaci antiretrovirali per la terapia dell'infezione da HIV-1, warfarin, ciclosporina, teofillina, digossina, contraccettivi orali. É altresì da evitare l'assunzione contemporanea di iperico con altre terapie farmacologiche antidepressive.

Effetti indesiderati

In rari casi lievi disturbi gastrointestinali, reazioni allergiche a carico della pelle, stanchezza o agitazione.

Note Bibliografiche

Composizione

Componenti caratteristici dell'Iperico sono dei derivati naftodiantronici globalmente indicati con il nome di "ipericine" e principalmente costituito da ipericina e pseudoipericina, oltre a piccole quantità di isoipericina, protoipericina e ciclopseudoipericina. Secondo la monografia della Farmacopea Europea (Hyperici Herba) la droga utilizzata a scopi medicinali deve contenere non meno dello 0,08 per cento di ipericina totale calcolate come ipericina ($C_{30}H_{16}O_8$; Mw 504,4)[1]. Altri composti importanti, contenuti nella frazione lipofila del fitocomplesso, sono iperforina e adiperforina, un gruppo di floroglucinoli prenilati chimicamente molto sensibili alla luce e al calore; sono altresì presenti i loro derivati ossigenati quali furoiperforina, deossifuroiperforina, ortoforina e adifuroiperforina. Sono inoltre presenti flavonoli glicosidi, tra cui iperoside (quercetin-3-galattoside), quercitrina, isoquercitrina e rutina, oltre a quercetina libera, quercetina-3-O-β-D-glucuronopiranoside e quercetina-3-xiloside; biflavoni, quali I3,II8-biapigenina e I3',II8-biapigenina (amentoflavone); fenilpropanoidi quali acido clorogenico ed altri esteri caffeoilchinici e p-cumaroilchinici; tannini condensati e proantocianidine oligomeriche, xantoni (1,3,5,6 tetraidrossixantone e kielcorina C); olio essenziale costituito prevalentemente da n-alcani a lunga catena (2-metil-ottano, nonano, 3-metil-nonano, undecano, dodecanolo) e, in quantità minori, da idrocarburi monoterpenici (alfa-pinene, cariofillene, beta-pinene, ecc.) e sesquiterpenici[2].

Farmacocinetica

In seguito a somministrazione orale di una dose singola di estratto standardizzato allo 0,3%, l'ipericina è rilevabile nel plasma dopo 1-3 ore dall'assunzione; la massima concentrazione ematica viene raggiunta in 4-6 ore. L'assorbimento dell'ipericina avviene nel tratto distale dell'intestino e non è dipendente dal tipo di formulazione dell'estratto. L'emivita plasmatica risulta di 25-28 ore circa. Sia l'emivita sia il t(max) sono indipendenti dalla dose. In seguito a somministrazione ripetuta (3x300 mg di estratto al giorno per 14 giorni) non sono stati osservati fenomeni di accumulo dell'ipericina nel plasma e l'emivita è risultata simile a quella dopo somministrazione singola. I livelli sistemici di equilibrio (steady-state) sono raggiunti entro 4 giorni dall'inizio del trattamento. La farmacocinetica dell'ipericina risulta lineare fino alla somministrazione di una dose pari a 600 mg di estratto e la biodisponibilità è circa del 14% La pseudoipericina raggiunge, dopo somministrazione singola per os, le concentrazioni plasmatiche massime in 0,5-1,5 ore e presenta una emivita plasmatica di 18-24 ore. La biodisponibilità è di circa il

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1 *St. John's Wort - Hyperici herba. European Pharmacopoeia, Council of Europe.*

2 "The chemical composition of St. John's wort has been well-studied." *(Barnes J, Anderson LA, Phillipson JD. St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties. J Pharm Pharmacol. 2001 May;53(5):583-600).*

21%[3]. Per quanto riguarda l'iperforina, il livello plasmatico massimo dopo somministrazione orale di una dose singola di estratto (standardizzato al 4,5% di iperiforina) si raggiunge dopo 3-3,5 ore. L'emivita terminale è di 9-12 ore circa. In seguito a somministrazione ripetuta non è stato osservato accumulo di iperforina nel plasma[4].

Attività biologiche ed impieghi clinici descritti in letteratura

Le attività biologiche e gli impieghi clinici descritti per l'*Hypericum perforatum* sono:

Medicina popolare. Il nome con cui l'Iperico è conosciuto in tutto il mondo è "St. John's Worth" (Erba di S. Giovanni), che si deve all'antica tradizione popolare che voleva che la pianta fosse colta il 24 giugno, giorno della festa di S. Giovanni Battista. Noto anche come "fugademonum" (scacciadiavoli), nella medicina popolare Europea - dal Mediterraneo alla Gran Bretagna - l'Iperico era impiegato contro la malinconia, gli sbalzi d'umore, l'agitazione nervosa e alcune forme di isterismo, che un tempo – prima che la depressione e le malattie psichiatriche venissero identificate come patologie dai connotati precisi – venivano attribuite ad influssi malefici. Veniva inoltre tradizionalmente utilizzato contro le nevralgie, negli stati infiammatori dei bronchi e delle vie genito-urinarie, come antidiarroico (probabilmente per l'azione astringente dei tannini), come diuretico (probabilmente per l'azione di alcuni flavonoidi), contro l'enuresi notturna e i reumatismi. Molto diffuso, inoltre, l'impiego topico del macerato oleoso (Oleum Hyperici) come vulnerario e per il trattamento delle scottature.

Sindrome depressiva e disturbi ansioso-depressivi. Tra le proprietà farmacologiche descritte in letteratura per gli estratti di Iperico l'azione antidepressiva rappresenta senz'altro quella di maggior rilievo clinico; parallelamente, sono stati inoltre osservati per la droga effetti moderatamente ansiolitici. Il meccanismo di azione, non ancora completamente noto, sarebbe comunque in larga parte da ricondurre ad attività sui neurotrasmettitori cerebrali anche se alcuni studi recenti suggeriscono ulteriori ed interessanti ipotesi. L'ottimo profilo di tollerabilità riscontrato contribuisce senza dubbio all'elevata compliance osservata nel corso degli studi e conferisce sicuramente un vantaggio clinico rispetto ad altri antidepressivi con un profilo di effetti collaterali meno favorevole.
In Germania l'Iperico è ufficialmente approvato dal 1984 per il trattamento della depressione e dell'agitazione nervosa e la prima monografia scientifica ufficiale emessa sulla droga è stata proprio quella della Commissione E tedesca[5]. Più recentemente l'ESCOP (European Scientific Cooperative

[3] *Wurglics M, Schubert-Zsilavecz M. Hypericum perforatum: a 'modern' herbal antidepressant: pharmacokinetics of active ingredients. Clin Pharmacokinet. 2006;45(5):449-68.*

[4] *Schulz HU, Schürer M, Bässler D, Weiser D. LAFAA Investigation of the bioavailability of hypericin, pseudohypericin, hyperforin and the flavonoids quercetin and isorhamnetin following single and multiple oral dosing of a hypericum extract containing tablet. Arzneimittelforschung. 2005; 55(1):15-22.*

[5] La Commissione E è un comitato scientifico della ex Agenzia Federale Tedesca per la Sanità impegnata dal 1978 nella valutazione della sicurezza e dell'efficacia dei farmaci a base di erbe. Pubblicata il 5 dicembre 1984 nel Bundesanzeiger (Gazzetta Ufficiale Federale), quella dell'iperico (Hyperici herba – Johanniskraut) è stata una delle prime monografie pubblicate dalla

on Phytotherapy, EU 2003), nella monografia dedicata alla pianta, ne raccomanda l'impiego per le seguenti indicazioni: "Episodi depressivi da lievi a moderati in conformità con le categorie ICD-10: F32.0, F32.1, F33.0 e F33.1"[6]. L'efficacia e la sicurezza degli estratti standardizzati di Iperico sono state valutate in almeno 40 studi clinici controllati di buon livello che hanno coinvolto circa 6000 pazienti; studi di monitoraggio farmacologico e numerosi studi osservazionali in aperto sono stati condotti su ulteriori decine di migliaia di pazienti. In molte di queste sperimentazioni è stato dimostrato un miglioramento significativo dei sintomi principali (umore depresso, perdita di interesse, ecc.) come anche di altri sintomi tipici della sindrome depressiva (sonno, concentrazione, disturbi somatici), e l'attività è stata studiata sia in confronto con farmaci antidepressivi classici (imipramina, amitriptilina, maprotilina) che di più recente concezione (fluoxetina, sertralina, paroxetina, citalopram)[7].

Le preparazioni di Iperico utilizzate per gli studi clinici sono estratti secchi idroetanolici 50-60% v/v ed estratti secchi idrometanolici 80% v/v. In particolare, i migliori studi condotti fino ad ora hanno utilizzato estratti secchi designati dalla letteratura clinica come LI 160, ZE 117, WS 5570. La dose terapeutica dell'Iperico come antidepressivo corrisponde ad un quantitativo di estratto secco idroalcolico il cui contenuto (in milligrammi) nella dose giornaliera di preparato equivalga, in base al rapporto droga/estratto, a 2-4 grammi di droga. Ciò corrisponde ad un quantitativo di estratto pari a 300-1000 mg/die. Sono necessarie circa due settimane per un primo riscontro dell'efficacia del preparato, così come accade per gli antidepressivi triciclici. In seguito gli effetti si manifestano con una crescita continua fino alla quarta settimana, dopodiché l'effetto si stabilizza sui livelli raggiunti.

I risultati degli studi sperimentali in modelli biochimici in vitro e in vivo e degli studi comportamentali sull'animale hanno dimostrato come diverse classi di composti contribuiscano sinergicamente all'effetto dell'estratto, evidenziando una notevole attività dell'iperforina[8], dei naftodiantroni e di

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Commissione E nel corso dei suoi 12 anni di attività. La monografia è stata successivamente tradotta dal Consiglio Botanico Americano *(Bluementhal et al, 1998)*

[6] La normativa relativa alle prove cliniche sugli antidepressivi, condivisa sia dalle autorità ministeriali europee che dall'FDA statunitense, prevede la classificazione dei pazienti secondo le chiavi diagnostiche internazionali DSM-VI (Diagnostic and Statistic Manual of Mental Disorders) oppure ICD-10.

[7] *Boncompagni E, Mercati V. L'iperico che cambia l'umore. Dalla tradizione millenaria ai moderni impieghi clinici in medicina e psichiatria. Aboca Edizioni, 2009.*

[8] "Hyperforin, a bicyclic polyprenylated acylphloroglucinol derivative, is the main active principle of St. John's wort extract responsible for its antidepressive profile. **Hyperforin inhibits the neuronal serotonin and norepinephrine uptake comparable to synthetic antidepressants. In contrast to synthetic antidepressants directly blocking neuronal amine uptake, hyperforin increases synaptic serotonin and norepinephrine concentrations by an indirect and yet unknown mechanism**. Our attempts to identify the molecular target of hyperforin resulted in the identification of TRPC6. Hyperforin induced sodium and calcium entry as well as currents in TRPC6-expressing cells. Sodium currents and the subsequent breakdown of the membrane sodium gradients may be the rationale for the inhibition of neuronal amine uptake. The hyperforin-induced cation entry was highly specific and related to TRPC6 and was suppressed in cells expressing a dominant negative mutant of TRPC6, whereas phylogenetically related channels, i.e., TRPC3 remained unaffected. Furthermore, hyperforin induces neuronal axonal sprouting like nerve growth factor in a TRPC6-dependent manner. T**hese findings support the role of TRPC channels in neurite extension and identify hyperforin as the first selective pharmacological tool to study TRPC6 function. Hyperforin integrates inhibition of neurotransmitter uptake and neurotrophic property by specific activation of TRPC6 and**

alcuni flavonoidi tra cui l'amentoflavone e la quercetina[9]. Tali evidenze sembrano confermare che è l'estratto totale l'effettivo "principio attivo" delle preparazioni a base della droga.

Le sostanze contenute nel fitocomplesso di *Hypericum perforatum* inibiscono l'uptake neuronale dei neurotrasmettitori, in particolare della serotonina, della noradrenalina, della dopamina e del GABA praticamente con analoga potenza, risultando quindi l'iperico l'unico antidepressivo che esibisce un profilo della captazione così ampio[10].

L'iperforina risulta il componente che inibisce in maniera più pronunciata l'uptake dei neurotrasmettitori (particolarmente della serotonina) e la sua attività, misurata con estratti a vario contenuto del principio attivo, risulta dose-dipendente. Estratti etanolici con quantitativi di iperforina inferiori allo 0,1% sembrano mostrare una selettività maggiore sulla ricaptazione della noradrenalina, similmente agli

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represents an interesting lead-structure for a new class of antidepressants." *(Leuner K, Kazanski V, Müller M, Essin K, Henke B, Gollasch M, Harteneck C, Müller WE. Hyperforin--a key constituent of St. John's wort specifically activates TRPC6 channels. FASEB J. 2007 Dec;21(14):4101-11).*

9 "Over the last few years m**any data have been published suggesting a participation of quercetin flavonoids in the antidepressive effect of St. John's wort (SJW) extract. To elucidate these data more deeply we performed two animal behavioural studies examining the antidepressant effects of SJW extract, rutin and, in addition, the quercetin metabolite isorhamnetin**. The substances were in all cases compared to imipramine using Porsolt's forced swimming test (FST) after oral gavage of the substances over a 9 day period. **All three compounds were found to be effective, with isorhamnetin exhibiting the strongest effect.** In addition to this pharmacological study, we carried out two pharmacokinetic studies to examine the CNS level time-curve of the quercetin flavonoids after a single oral dose of SJW extract (1600 mg/kg) and isoquercitrin (100 mg/kg), respectively, and to observe the cumulative effects after daily repeated oral doses of SJW extract over 8 days. After a single dose the maximal CNS levels for quercetin (340 ng/g) and isorhamnetin/tamarixetin (50 ng/g) were found at 4 h. With repeated doses the maximal cumulation for quercetin (367 ng/g) occurred after 5 days whilst isorhamnetin/tamarixetin (640 ng/g) did not reach its maximal cumulation level within the 8 day test period." *(Paulke A, Nöldner M, Schubert-Zsilavecz M, Wurglics M. St. John's wort flavonoids and their metabolites show antidepressant activity and accumulate in brain after multiple oral doses. Pharmazie. 2008 Apr;63(4):296-302).*

10 "Extracts of Hypericum perforatum L. (St John's wort) are now successfully competing for status as a standard antidepressant therapy. Because of this, great effort has been devoted to identifying the active antidepressant compounds in the extract. From a phytochemical point of view, St John's wort is one of the best-investigated medicinal plants. A series of bioactive compounds has been detected in the crude material, namely flavonol derivatives, biflavones, proanthocyanidines, xanthones, phloroglucinols and naphthodianthrones. Although St John's wort has been subjected to extensive scientific studies in the last decade, there are still many open questions about its pharmacology and mechanism of action. **Initial biochemical studies reported that St John's wort is only a weak inhibitor of monoamine oxidase-A and -B activity but that it inhibits the synaptosomal uptake of serotonin, dopamine and noradrenaline (norepinephrine) with approximately equal affinity. However, other in vitro binding assays carried out using St John's wort extract demonstrated significant affinity for adenosine, GABA(A), GABA(B) and glutamate receptors. In vivo St John's wort extract leads to a downregulation of beta-adrenergic receptors and an upregulation of serotonin 5-HT(2) receptors in the rat frontal cortex and causes changes in neurotransmitter concentrations in brain areas that are implicated in depression.** In studies using the rat forced swimming test, an animal model of depression, St John's wort extracts induced a significant reduction of immobility. In other experimental models of depression, including acute and chronic forms of escape deficit induced by stressors, **St John's wort extract was shown to protect rats from the consequences of unavoidable stress. Recent neuroendocrine studies suggest that St John's wort is involved in the regulation of genes that control hypothalamic-pituitary-adrenal axis function.** With regard to the antidepressant effects of St John's wort extract, **many of the pharmacological activities appear to be attributable to the naphthodianthrone hypericin, the phloroglucinol derivative hyperforin and several flavonoids.** This review integrates new findings of possible mechanisms that may underlie the antidepressant action of St John's wort and its active constituents with a large body of existing literature." *(Butterweck V. Mechanism of action of St John's wort in depression: what is known? CNS Drugs. 2003;17(8):539-62).*

antidepressivi triciclici[11]. Ciò sembrerebbe confermato da uno studio effettuato su ratti sottoposti al forced swimming test. Si è notato che gli animali trattati con iperico nuotavano più di quelli che ricevevano il placebo, e che tale effetto era antagonizzato dalla sulpiride, che come noto è un dopamino-antagonista[12]. È anche interessante notare che l'Iperico possiede un effetto reserpino-antagonista a livello centrale: infatti il calo della temperatura corporea indotto dalla reserpina viene antagonizzato dall'estratto di iperico, indipendentemente dall'ordine di somministrazione delle due sostanze. Questo effetto è tipico anche dell'amineptina, un antidepressivo a prevalente attività dopaminergica centrale. Infine, l'estratto di Iperico nel topo riduce, in modo dose-dipendente, il tempo di sonno indotto dalla chetamina con un effetto paragonabile a quello del bupropione, un antidepressivo che inibisce la ricaptazione della dopamina. Ciò è un ulteriore supporto all'ipotesi che l'azione dopamino-agonista sia importante per spiegare l'effetto farmacologico dell'iperico, soprattutto considerando che il potenziamento della trasmissione dopaminergica è un risultato comune a diversi trattamenti antidepressivi sia classici (triciclici) che di più recente concezione. L'estratto totale di Iperico mostra una significativa affinità per i recettori del GABA, sia di tipo A sia di tipo B. Tra i vari componenti, l'amentoflavone si è dimostrato quello più attivo sui recettori GABA-A inibendo, in vitro, il legame delle benzodiazepine a concentrazioni che rientrano nel range

[11] "Despite almost forty years of widespread use, the mode of action of antidepressant drugs is still largely unknown. There is agreement that these drugs interact with central neurotransmission. Common findings are acute inhibitory actions on reuptake mechanisms for norepinephrine (NE) and for serotonin (5-HT) at presynaptic axons and chronic adaptive effects on neurotransmitter receptors on postsynaptic membranes. In particular, beta-adrenoceptor downregulation has been observed after chronic treatment with most antidepressants in vivo and in cell culture systems. **We studied the effectiveness of Ze 117 (St. John's wort) extract (Hypericum perforatum) on NE- and 5-HT-uptake into rat brain slices. Potency and efficacy of the Ze 117 extract were compared with those of tricyclic (TCA) and selective serotonin reuptake inhibitor (SSRI)-type antidepressants. A dose-dependent inhibition was seen on NE and 5-HT uptake into brain slices. The Ze 117 extract was more selective for the uptake of NE than for that of 5-HT. The maximal extent of uptake inhibition by Ze 117 extract was comparable to that of imipramine (IMI), desipramine (DMI) or fluvoxamine for 5-HT, but lower for NE transport, than that of the synthetic antidepressants. Chronic exposure (8 days) of confluent C6-cell cultures to Ze 117 extract resulted in a dose-dependent beta-adrenoceptor downregulation equal to that induced by DMI, a potent TCA**. None of these effects could be achieved with either hypericin or hyperforin alone in a relevant dose range." *(Kientsch U, Bürgi S, Ruedeberg C, Probst S, Honegger UE. St. John's wort extract Ze 117 (Hypericum perforatum) inhibits norepinephrine and serotonin uptake into rat brain slices and reduces 3-adrenoceptor numbers on cultured rat brain cells. Pharmacopsychiatry. 2001 Jul;34 Suppl 1:S56-60).*

[12] "The effects of hydro-alcoholic extracts of Hypericum perforatum L on extracellular serotonin (5-HT), noradrenaline (NA) and dopamine (DA) levels and the acidic metabolites (3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxy-3-indoleacetic acid (5-HIAA)) were examined by in vivo microdialysis in the prefrontal cortex of awake rats. Thus, **a single dose (60 mg kg(-1) i.p. or 300 mg kg(-1) p.o.) of H. perforatum increased DA concentrations to 165 and 140% of control values, respectively, and increased locomotor activity in nonhabituated rats. DOPAC and HVA levels were markedly reduced. 5-HT concentrations were elevated only moderately, while the NA levels were not affected by any treatment**. The whole-tissue analysis revealed that hypericum increased, whereas the monoamine oxidase (MAO) A/B inhibitor phenelzine decreased DA and 5-HT turnover. The present data indicate that **the mechanism of action of hypericum extract in vivo is more complex than the inhibition of monoamine reuptake or metabolism observed in vitro. The finding of preferential enhancement of DA transmission is in agreement with human studies measuring DA-mediated neuroendocrine responses**." *(Yoshitake T, Iizuka R, Yoshitake S, Weikop P, Müller WE, Ogren SO, Kehr J. Hypericum perforatum L (St John's wort) preferentially increases extracellular dopamine levels in the rat prefrontal cortex. Br J Pharmacol. 2004 Jun;142(3):414-8).*

del dosaggio terapeutico dell'estratto[13]. È noto che la trasmissione GABAergica è coinvolta nella regolazione del tono dell'umore, per cui la sua modulazione potrebbe avere un ruolo nell'attività antidepressiva. La stimolazione dei recettori GABA-B, ad esempio, potenzia la desensibilizzazione dei recettori beta-adrenergici indotta dall'imipramina ed è descritta l'attività antidepressiva di un agente GABAergico come la fengabina. Inoltre è stato riportato che i livelli plasmatici di GABA sono ridotti nei pazienti unipolari e bipolari e che le benzodiazepine (farmaci potenzianti la trasmissione GABAergica) possiedono una certa attività antidepressiva, oltre a quella ansiolitica. L'effetto sui recettori del GABA potrebbe spiegare anche gli effetti ansiolitici riscontrati per la droga.

I dati relativi al meccanismo d'azione dell'iperforina indicano che l'azione inibitoria del reuptake non coinvolge specifici siti di legame a livello dei recettori dei neurotrasmettitori, suggerendo che l'effetto centrale dell'iperforina potrebbe essere indirettamente mediato da un metabolita o da un neuromodulatore che interagisce con il recettore sigma, oppure che la molecola potrebbe agire a livello periferico modulando i livelli di interleuchina-6 (IL-6) circolante, in accordo con l'ipotesi secondo cui l'ipersecrezione di citochine potrebbe essere coinvolta nell'insorgenza e nel mantenimento dei disordini depressivi[14]. L'inibizione dell'IL-6, con conseguente riduzione della produzione ipotalamica di CRF, potrebbe essere importante per spiegare, almeno in parte, l'aumento della serotonina indotto dall'estratto di Iperico[15]. Da studi neuroendocrini in vitro si evince inoltre che l'aumento del CRF

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13 "**We investigated the recognition properties of different GABA(A) receptor subtypes and mutant receptors for the biflavonoid amentoflavone, a constituent of St. John's Wort. Radioligand binding studies showed that amentoflavone recognition paralleled that of the classical benzodiazepine diazepam in that it had little or no affinity for alpha4- or alpha6-containing receptors**. Lysine and alanine substitutions at position 101 of the rat alpha1 subunit resulted in a complete loss of competitive amentoflavone binding, but functional analysis of the alanine mutant expressed with beta2 and gamma2 subunits in Xenopus oocytes revealed no significant difference in the negative modulation of GABA-induced currents brought about by amentoflavone. Furthermore, elimination of the gamma subunit had no effect on the negative modulation of these currents. This negative modulation was also observed at alpha1beta1gamma2 GABA(A) receptors and is therefore not likely mediated by the loreclezole site. **These results suggest a complex mechanism of amentoflavone interaction at GABA(A) receptors**." *(Hansen RS, Paulsen I, Davies M. Determinants of amentoflavone interaction at the GABA(A) receptor. Eur J Pharmacol. 2005 Sep 20;519(3):199-207).*

14 "Clinical data indicate that hydroalcoholic extracts of Hypericum perforatum might be as valuable as conventional antidepressants in mild-to-moderate depression, with fewer side effects. One clinical trial using two extracts with different hyperforin contents indicated it as the main active principle responsible for the antidepressant activity. Behavioural models in rodents confirm the antidepressant-like effect of Hypericum extracts and also of pure hyperforin and hypericin. A hydroalcoholic extract lacking hyperforin also lacks the antidepressant-like effect. According to pharmacokinetic data and binding studies, it appears that the antidepressant effect of Hypericum extract is unlikely be due to an interaction of hypericin with central neurotransmitter receptors. **The main in vitro effects of hyperforin (at concentrations of 0.1-1 microM) are non-specific presynaptic effects, resulting in the non-selective inhibition of the uptake of many neurotransmitters, and the interaction with dopamine D1 and opioid receptors. However, it is still not clear whether these mechanisms can be activated in vivo, since after administration of Hypericum extract brain concentrations of hyperforin are well below those active in vitro. In the rat, Hypericum extract might indirectly activate sigma receptors in vivo (through the formation of an unknown metabolite or production of an endogenous ligand), suggesting a new target for its antidepressant effects**." *(Mennini T, Gobbi M. The antidepressant mechanism of Hypericum perforatum. Life Sci. 2004 Jul 16;75(9):1021-7).*

15 "**The aim of the present study was to evaluate the mechanisms of action of the standardized St. John's wort extract (STW3-VI; SJW) in a chronic restraint stress model.** Markers of antioxidant capacity such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) in the hippocampus and hypothalamus, and plasma levels of ACTH and

viene contrastato anche dalla pseudoipericina, che ha dimostrato un'azione antagonista diretta sui recettori CRF1[16]. La modulazione della funzione ipotalamo-ipofisi-surrenalica potrebbe essere uno dei meccanismi più rilevanti dell'azione antidepressiva dell'iperico[17]. Riguardo all'azione inibitoria sulla ricaptazione neuronale sono stati suggeriti anche altri meccanismi d'azione, che coinvolgono sia la funzione dei sinaptosomi e delle vescicole di deposito dei neurotrasmettitori[18] sia la conduttanza ionica[19]. Recenti ricerche indicano infatti che l'iperforina influisce in modo notevole sui flussi ionici

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corticosterone as well as the inflammatory markers IL-6 and TNF-alpha were determined in rats exposed to chronic restraint stress for 21 consecutive days. In addition, total body and relative organ weights as well as behavioral changes in the open field test were evaluated on the last day. **The results show that stressed animals decreased in open field activity compared to unstressed animals, which could be reversed by fluoxetine (10mg/kg, p.o.) and SJW (125-750mg/kg, p.o.) treatment. In addition, chronic restraint stress significantly decreased thymus and spleen indices in the stressed control group. However, treating stressed rats with fluoxetine or STW3-VI produced a significant and dose dependent increase in both thymus and spleen indices compared to stressed controls. Additionally, SJW and fluoxetine significantly reduced stress-induced increases in plasma ACTH and corticosterone levels. Furthermore, the administration of SJW significantly reduced the stress-induced increase in TNF-alpha levels. Our data provide new evidence for the hypothesis that the mechanism of action of STW3-VI is mediated by the interrelationship between the immune, oxidative defense and neuroendocrine system**." *(Grundmann O, Lv Y, Kelber O, Butterweck V. Mechanism of St. John's wort extract (STW3-VI) during chronic restraint stress is mediated by the interrelationship of the immune, oxidative defense, and neuroendocrine system. Neuropharmacology. 2009 Dec 28. [Epub ahead of print]).*

16 "It has been suggested repeatedly in preclinical and clinical studies that the content of the acylphloroglucinol hyperforin decisively contributes to the antidepressant efficacy of St. John's wort extracts. **Experimental studies in vivo also indicate that the naphthodianthrone hypericin may reduce the activity of the hypothalamic-pituitary-adrenal axis. Exacerbated hypothalamic-pituitary-adrenal activity has often been associated with depressive states in patients.** Corticotropin-releasing factor (CRF) seems to be a major determinant in the regulation of the hypothalamic-pituitary-adrenal activity via activation of CRF(1) receptors…" *(Simmen U, Bobirnac I, Ullmer C, Lübbert H, Berger Büter K, Schaffner W, Schoeffter P. Antagonist effect of pseudohypericin at CRF1 receptors. Eur J Pharmacol. 2003 Jan 5;458(3):251-6).*

17 *Butterweck V. Mechanism of action of St John's wort in depression: what is known? CNS Drugs. 2003;17(8):539-62.*

18 "Hyperforin is the major active ingredient of Hypericum perforatum (St John's Wort), a traditional antidepressant medication. This study evaluated its inhibitory effects on the synaptic uptake of monoamines in rat forebrain homogenates, comparing the nature of the inhibition at synaptic and vesicular monoamine transporters. **A hyperforin-rich extract inhibited with equal potencies the sodium-dependent uptake of the monoamine neurotransmitters serotonin [5-HT], dopamine [DA] and norepinephrine [NE] into rat brain synaptosomes. Hyperforin inhibited the uptake of all three monoamines noncompetitively**, in marked contrast with the competitive inhibition exerted by fluoxetine, GBR12909 or desipramine on the uptake of these monoamines. Hyperforin had no inhibitory effect on the binding of [3H]paroxetine, [3H]GBR12935 and [3H] nisoxetine to membrane presynaptic transporters for 5-HT, DA and NE, respectively. **The apparent presynaptic inhibition of monoamine uptake could reflect a "reserpine-like mechanism" by which hyperforin induced release of neurotransmitters from synaptic vesicles into the cytoplasm. Thus, we assessed the effects of hyperforin on the vesicular monoamine transporter. Hyperforin inhibited with equal potencies the uptake of the three tritiated monoamines to rat brain synaptic vesicles. Similarly to the synaptosomal uptake, the vesicular uptake was also noncompetitively inhibited by hyperforin.** Notably, hyperforin did not affect the direct binding on [3H]dihydrotetrabenazine, a selective vesicular monoamine transporter ligand, to rat forebrain membranes. **Our results support the notion that hyperforin interferes with the storage of monoamines in synaptic vesicles, rather than being a selective inhibitor of either synaptic membrane or vesicular monoamine transporters.**" *(Roz N, Mazur Y, Hirshfeld A, Rehavi M. Inhibition of vesicular uptake of monoamines by hyperforin. Life Sci. 2002 Sep 27;71(19):2227-37).*

19 "Hyperforin is currently considered to be the major active antidepressant constituent of the medicinal herb St. John's wort (Hypericum perforatum L.). The mechanism of action however, is still largely unknown, although **the involvement of sodium and calcium has been recently inferred.** In the present study hyperforin (5 microM) significantly potentiated the release of endogenous aspartate and glutamate from mouse cortical slices when stimulated by veratridine or potassium. Hyperforin (5

delle cellule nervose, in particolare in quelle dei nuclei della base e soprattutto del nucleo arcuato: sembra che essa sia in grado di inibire il reuptake della serotonina innalzando i livelli intracellulari di Na^+ già a concentrazioni molto basse, che non si legano alle proteine di trasporto. Da questi dati sembrerebbe che il meccanismo dell'inibizione serotoninica dell'iperforina possa essere legato ad un meccanismo aspecifico di alterazione dell'omeostasi ionica, differendo quindi da quello degli antidepressivi classici come SSRI e triciclici.

È interessante notare, tuttavia, che gli effetti più significativi dell'Iperico sui livelli cerebrali di neurotrasmettitori sono osservabili in seguito a somministrazione a lungo termine, suggerendo l'ipotesi che sono necessarie una serie di modificazioni adattative nella neurotrasmissione affinché l'azione terapeutica dell'estratto si manifesti appieno, proprio come per gli antidepressivi di sintesi[20]. La variazione dell'espressione di recettori delle monoamine è un'altro dei meccanismi dell'Iperico riconducibile a modificazioni adattative nella neurotrasmissione. In seguito a trattamento subacuto con estratto metanolico di *Hypericum perforatum* per 14 giorni, oltre ad aumento della concentrazione sinaptica di neurotrasmettitori è stata osservata nei ratti una significativa down-regulation dei β-adrenorecettori nella corteccia frontale, un risultato caratteristico di molti farmaci antidepressivi. Il simultaneo e significativo aumento del numero dei recettori serotoninergici 5-HT2 riscontrato è risultato invece in contrasto con gli effetti di molti antidepressivi classici[21]. L'unico altro trattamento antidepressivo che provoca questo effetto a lungo termine nell'animale è il trattamento elettroconvulsivo (elettroshock), impiegato nei casi più gravi di depressione resistente. Ancora, alcuni componenti dell'estratto di *Hypericum perforatum* – tra cui la frazioni xantonica dell'estratto

microM) also stimulated the release of aspartate, glutamate, serine, glycine and GABA when perfused on its own. Perfusion of the sodium channel blocker, tetrodotoxin (TTX) inhibited the effect of hyperforin, whereas removal of extracellular calcium potentiated the effect. **Our observations suggests that hyperforin increases the overflow of neurotransmitters from mouse cerebral cortex possibly through facilitating the entry of sodium into the neurone which leads to the release of calcium from intracellular stores.**" *(Roz N, Mazur Y, Hirshfeld A, Rehavi M. Inhibition of vesicular uptake of monoamines by hyperforin. Life Sci. 2002 Sep 27;71(19):2227-37).*

[20] "Hypericum perforatum L. (St. John's wort) is one of the leading psychotherapeutic phytomedicines and, because of this, great effort has been devoted to clarifying its mechanism of action. **Chronic effects of St. John's wort and hypericin, one of its major active compounds, on regional brain amine metabolism have not been reported yet**. **We used a high-performance liquid chromatography system to examine the effects of short-term (2 weeks) and long-term (8 weeks) administration of imipramine, Hypericum extract or hypericin on regional levels of serotonin (5-HT), norepinephrine, dopamine and their metabolites in the rat brain. We focused our interest on the hypothalamus and hippocampus, as these brain regions are thought to be involved in antidepressant drug action.** Imipramine (15 mg/kg, p.o.), Hypericum extract (500 mg/kg, p.o.), and hypericin (0.2 mg/kg, p.o.) given daily for 8 weeks significantly increased 5-HT levels in the hypothalamus ($P<0.05$). The 5-HT turnover was significantly lowered in both brain regions after 8 weeks of daily treatment with the Hypericum extract (both $P<0.05$). Consistent changes in catecholamine levels were only detected in hypothalamic tissues after long-term treatment. **Comparable to imipramine, Hypericum extract as well as hypericin significantly decreased 3,4-dihydroxyphenylacetic acid and homovanillic acid levels in the hypothalamus ($P<0.01$). Our data clearly show that long-term, but not short-term administration of St. John's wort and its active constituent hypericin modify levels of neurotransmitters in brain regions involved in the pathophysiology of depression.**" *(Butterweck V, Böckers T, Korte B, Wittkowski W, Winterhoff H. Long-term effects of St. John's wort and hypericin on monoamine levels in rat hypothalamus and hippocampus. Brain Res. 2002 Mar 15;930(1-2):21-9).*

[21] *Teufel-Mayer R, Gleitz J. Effects of long-term administration of hypericum extracts on the affinity and density of the central serotonergic 5-HT1 A and 5-HT2 A receptors. Pharmacopsychiatry. 1997 Sep;30 Suppl 2:113-6.*

e i flavonoidi, in particolare quercetina e isoquercitroside – hanno inibito le monoaminoossidasi (MAO); tuttavia, ricerche successive hanno evidenziato che la concentrazione raggiunta in vivo da tali componenti è troppo bassa per poter esplicare un effetto terapeutico[22]. Altri studi hanno dimostrato che l'Iperico è in grado di inibire anche le catecol-O-metiltransferasi (COMT), ma anche in questo caso a dosaggi però relativamente elevati[23]. Gli studi in vivo nell'uomo riportano che, come per altri antidepressivi (amitriptilina, desipramina), in seguito a somministrazione prolungata di estratto di Iperico (su volontari per 3 settimane) si verifica un aumento della soppressione di melatonina indotta dalla luce e un significativo aumento della concentrazione notturna di melatonina nel plasma. Gli effetti dell'estratto di Iperico sulla qualità del sonno sono stati confrontati con quelli degli antidepressivi triciclici e dei MAO-inibitori non selettivi, che causano un prolungamento della latenza della fase REM ed una soppressione della fase del sonno REM. I risultati dimostrano che il trattamento con Iperico produce una leggera riduzione (ca. 10 min.) nella latenza del sonno REM lasciando invece inalterata la proporzione del sonno REM rispetto alla durata totale del sonno. È stato inoltre osservato un aumento nella fase ad onde lente negli stadi del sonno profondo (3 e 4)[24]. Questo risultato potrebbe essere correlato all'attività antidepressiva dell'Iperico, dal momento che diversi autori sostengono che una riduzione del sonno ad onde lente potrebbe essere un significativo indicatore neurobiologico nei disturbi dell'umore. In definitiva, possiamo concludere che l'azione antidepressiva dell'Iperico deriva dal concorso di molteplici meccanismi, ciascuno dei quali contribuisce in varia misura all'azione globale del fitocomplesso. Il risultato è un'azione terapeutica efficace e priva di rilevanti effetti collaterali[25]. È interessante anzi notare come il trattamento di lunga

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22 "The inhibition of monoamine oxidase (MAO) by six fractions from hypericum extract and three characteristic constituents (as pure substances) were analyzed in vitro and ex vivo to study the antidepressive mechanism of action… **From the results it can be concluded that the clinically proven antidepressive effect of hypericum extract cannot be explained in terms of MAO inhibition.**" *(Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of hypericum extract. J Geriatr Psychiatry Neurol 1994; Suppl 1: S57-9).*

23 "The influence of hypericin, hypericum total extract, and hypericum fractions on the activity of MAO and COMT, prepared in vitro from pork liver, were investigated in several concentration steps. **An inhibition of MAO could be shown in the following concentrations (extract correlated to a mean molecular value of 500): hypericin to 10(-3) mol/L, hypericum total extract to 10(-4) mol/L, one extract fraction up to 10(-5)**. A COMT inhibition could not be shown for hypericin, with hypericum extract to 10(-4) mol/L and with two extract fractions also up to 10(-4) mol/L… The concentrations of inhibition shown might not be sufficient to explain the clinically proven antidepressive effect of hypericum particularly with regard to the inhibition of MAO activity." *(Thiede HM, Walper A. Inhibition of MAO and COMT by hypericum extracts and hypericin. J Geriatr Psychiatry Neurol 1994; Suppl 1: S54-6).*

24 *Sharpley AL, McGavin CL, Whale R, Cowen PJ. Antidepressant-like effect of Hypericum perforatum (St John's wort) on the sleep polysomnogram. Psychopharmacology (Berl). 1998 Oct;139(3):286-7.*

25 "St. John's wort (Hypericum perforatum L., SJW) contains numerous compounds with documented biological activity. Constituents that have stimulated the most interest include the naphthodianthrones hypericin and pseudohypericin, a broad range of flavonoids, and the phloroglucinols hyperforin and adhyperforin. **According to the actual state of scientific knowledge the total extract has to be considered as the active substance. Although there are some open questions, the bulk of data suggests that several groups of active compounds are contributing to the antidepressant efficacy of the plant extract.**" *(Butterweck V, Schmidt M. St. John's wort: role of active compounds for its mechanism of action and efficacy. Wien Med Wochenschr. 2007;157(13-14):356-61).*

durata con *Hypericum perforatum* non alteri le funzioni cognitive del paziente[26]; addiritura, in alcune condizioni sperimentali è stato osservato un miglioramento dell'attenzione e della concentrazione nel volontario sano[27].

L'interesse del mondo medico per l'azione antidepressiva dell'Iperico è nato nel 1996, quando è apparsa sul British Medical Journal una metanalisi di 23 studi clinici controllati condotti su un totale di 1757 pazienti con depressione da lieve a moderata, 15 dei quali paragonavano gli estratti di *Hypericum perforatum* al placebo (1008 pazienti) e 8 ad altri antidepressivi (749 pazienti). Il dosaggio dell'estratto era di 300-1000 mg/die e il tempo di osservazione di 4-8 settimane. I risultati, valutati utilizzando test psicometrici standard come l'Hamilton Depression Rating Scale (HAMD), indicavano una chiara superiorità dell'iperico sul placebo e un'efficacia simile agli antidepressivi di confronto (imipramina[28] e maprotilina[29]). L'elevata tollerabilità riscontrata nel corso degli studi contribuì in maniera determinante all'interesse del mondo scientifico nei confronti della pianta. L'Iperico aveva dimostrato, nei vari studi sottoposti ad analisi comparata, una minima incidenza di drop-out e scarsissimi effetti collaterali. Gli autori concludevano che gli estratti di Iperico sono più efficaci del placebo per l'uso a breve termine nella depressione lieve e moderata e comparabili agli antidepressivi

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26 "In a placebo-controlled, randomized, double-blind trial involving outpatients with mild to moderately severe depression, an extract of St. John's wort (Hypericum), LI 160, a herbal antidepressant was tested for efficacy and tolerability, as well as for possible negative effects on cognitive performance… N**o impairment of cognitive performance was observed: during the trial, Hypericum did not lead to any impairment of attention, concentration or reaction.**" *(Schmidt U, Sommer H. St. John's wort extract in the ambulatory therapy of depression. Attention and reaction ability are preserved. Fortschr Med 1993; 111: 339-42).*

27 "In a randomized double-blind study, the effect of hypericum extract was compared to that of maprotiline in 24 healthy volunteers… In resting EEGs, both medications revealed oppositely directed changes in the theta frequencies, and mainly similarly directed changes in α and β frequencies. Measurements of evoked potentials in the theta and β frequencies supported these results. **The results indicate improved cognitive functions mainly with the treatment of hypericum extract.**" *(Johnson D, Ksciuk H, Woelk H, Sauerwein-Giese E, Frauendorf A. Effects of hypericum extract LI 160 compared with maprotiline on resting EEG and evoked potentials in 24 volunteers. J Geriatr Psychiatry Neurol 1994; Suppl 1:S44-6).*

28 "In a double-blind comparative study, 135 depressed patients were treated in 20 centers. Inclusion diagnoses were typical depressions with single episode (296.2), several episodes (296.3), depressive neurosis (300.4), and adjustment disorder with depressed mood (309.0) in accordance with DSM-III-R. The dosage was 3 x 300 mg hypericum extract LI 160 or 3 x 25 mg imipramine daily. The treatment lasted for 6 weeks… **The analysis of CGI revealed comparable results in both treatment groups**. Clinically relevant changes of the safety parameters were not found. **In the LI 160 group fewer and milder side effects were found as compared to imipramine.**" *(Vorbach EU, Hubner WD, Arnoldt KH. Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine: randomized double-blind study with 135 outpatients. J Geriatr Psychiatry Neurol 1994; Suppl 1: S19-23).*

29 "A randomized, double-blind study examining the effectiveness and tolerance of a standardized hypericum preparation when compared to maprotiline was performed in a group of 102 patients with depression, in accordance with ICD-10, F 32.1. The study was conducted in the offices of neurology and psychiatry specialists. The patients received, over a period of 4 weeks, either 3 x 300 mg of the hypericum extract or 3 x 25 mg maprotiline pills of identical appearance. Effectiveness was determined using the Hamilton Depression Scale (HAMD), the Depression Scale according to von Zerssen (D-S), and the Clinical Global Impression Scale(CGI)… **The total score of the HAMD scale dropped during the 4 weeks of therapy in both treatment groups by about 50%. The mean values of the D-S scale and the CGI scale showed similar results, and after 4 weeks of therapy, no significant differences in either treatment group were noticed… On the other hand, maprotiline treatment resulted in more cases of tiredness, mouth dryness, and heart complaints."** *(Harrer G, Hubner WD, Podzuweit H. Effectiveness and tolerance of the hypericum extract LI 160 compared to maprotiline: a multicenter double-blind study. J Geriatr Psychiatry Neurol 1994; Suppl 1: S24-8).*

triciclici[30]. Diverse altre metanalisi e rassegne sistematiche, condotte in anni successivi con criteri di inclusione ancora più selettivi e con farmaci di confronto più attuali, hanno sostanzialmente confermato questi risultati. In particolare, un successivo lavoro di metanalisi ha valutato i lavori clinici pubblicati fino alla primavera del 2002 includendo 34 studi clinici controllati in doppio cieco condotti su un totale di circa 3000 pazienti, sia *vs* placebo che *vs* attivo (imipramina, fluoxetina, maprotilina, sertralina). Gli autori concludono che l'Iperico è piuttosto simile ai farmaci antidepressivi come efficacia, mentre è decisamente migliore come tollerabilità[31]. Tra i vari lavori esaminati, uno studio che mette a confronto l'efficacia e la tollerabilità di 500 mg/die dell'estratto secco idroetanolico ZE 117 con l'inibitore selettivo del re-uptake della serotonina (SSRI) più comunemente usato (fluoxetina 20 mg/die; Schrader, 2000), in 240 pazienti con depressione di grado lieve-moderato con valori della scala HAMD (21 indicatori) nel range 16-24 (media 19,6): 126 (52%) assumevano Iperico e 114 (48%) di fluoxetina. I criteri di valutazione erano la scala di Hamilton per la depressione (HAMD), la Clinical Global Impression (CGI) e la scala di autovalutazione VAS (Visual Analogic Scale). Dopo 6 settimane di trattamento, la media del punteggio HAMD all'end-point si riduceva a 11,54 per l'Iperico e a 12,20 per la fluoxetina (P<0,09); cioè nel confronto con fluoxetina il 60% del braccio Iperico e il 40% del braccio fluoxetina mostrava un miglioramento di almeno il 50%. Anche la media dei punteggi della Clinical Global Impression era significativamente superiore per l'estratto di Iperico (p<0,005). Riguardo poi al profilo di tollerabilità, quello dell'Iperico era decisamente superiore, con un'incidenza di eventi avversi dell'8% contro il 23% riscontrato per la fluoxetina[32]. Risultati analoghi relativamente ad una

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30 *Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression--an overview and meta-analysis of randomised clinical trials. BMJ. 1996 Aug 3;313(7052):253-8.*

31 "**By the spring of 2002, results from 34 controlled, double-blind trials of Hypericum extracts in some 3000 patients, predominantly with mild to moderate forms of depression, had been published**. An overview is given of the studies conducted since 1990. In the majority of them, the efficacy criterion (primary endpoint) was the score and/or response rate on the Hamilton Rating Scale of Depression (HAMD). **In ten studies, based on extracts prepared with 50% or 60% ethanol in water (V/V), the dosages ranged from 300 mg to 1050 mg of extract per day. Five of the ten studies were placebo-controlled and in all five cases, the Hypericum extract was shown to be significantly superior. Results with Hypericum were as good or even better than with imipramine or fluoxetine.** In the period since 1990, a total of twelve controlled trials have been published with one particular extract prepared with 80% methanol in water (V/V), of which six were placebo-controlled, two compared Hypericum with imipramine and one each with maprotiline, amitriptyline, sertraline or light therapy. Dosages ranged from 450-1200 mg extract per day. Statistical analysis of the total Hamilton scores showed significant differences between Hypericum extract and placebo in four of the six placebo-controlled studies and a trend in favour of the active treatment in the other two. **Of the five comparative trials against four different synthetic antidepressants, amitriptyline was significantly superior to Hypericum after six weeks of therapy, whilst there were no significant differences in treatment outcome between Hypericum and the other synthetics in the remaining four studies**. The results of the trials conducted to date show no major differences in efficacy of the alcoholic extracts. Taking all the results into account, it can be assumed that the threshold dose for efficacy against individual symptoms and complaints that occur in the course of the depressive illness could be about 300 mg of extract per day. In the medically supervised treatment of mild to moderate depression, doses of approximately 500-1000 mg of extract per day of these preparations of St. John's Wort are of comparable efficacy to synthetic antidepressants in their normally prescribed dosages." *(Schulz V. Clinical trials with hypericum extracts in patients with depression--results, comparisons, conclusions for therapy with antidepressant drugs. Phytomedicine. 2002 Jul;9(5):468-74).*

32 "**Treatment with St John's wort extract tablets (hypericum Ze 117) and the commonly used slow serotonin reuptake inhibitor (SSRI) fluoxetine was compared in patients with mild-moderate depression with entry Hamilton Depression**

sostanziale equivalenza tra iperico e fluoxetina (a fronte di un migliore profilo di tollerabilità per l'estratto), sono stati ottenuti da almeno altri due lavori, sempre in pazienti con diagnosi di depressione lieve-moderata[33,34]. L'estratto di Iperico (WS 5770) è stato confrontato anche con altri SSRI, quali sertralina[35] e paroxetina[36], dimostrando anche in questi casi un'efficacia comparabile al farmaco. I

Scale (HAM-D) (21-item) in the range 16-24, in a randomized, double-blind, parallel group comparison in 240 subjects; fluoxetine: 114 (48%), hypericum: 126 (52%). After 6 weeks' treatment, mean HAM-D at endpoint decreased to 11.54 on hypericum and to 12.20 on fluoxetine (P < 0.09), while mean Clinical Global Impression (CGI) item I (severity) was significantly (P < 0.03) superior on hypericum, as was the responder rate (P = 0.005). Hypericum safety was substantially superior to fluoxetine, with the incidence of adverse events being 23% on fluoxetine and 8% on hypericum. The commonest events on fluoxetine were agitation (8%), GI disturbances (6%), retching (4%), dizziness (4%), tiredness, anxiety/nervousness and erectile dysfunction (3% each), while on hypericum only GI disturbances (5%) had an incidence greater than 2%. **We concluded that hypericum and fluoxetine are equipotent with respect to all main parameters used to investigate antidepressants in this population. Although hypericum may be superior in improving the responder rate, the main difference between the two treatments is safety. Hypericum was superior to fluoxetine in overall incidence of side-effects, number of patients with side-effects and the type of side-effect reported.**" *(Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. Int Clin Psychopharmacol. 2000 Mar;15(2):61-8).*

33 "**Efficacy and tolerability of Hypericum LI 160 was compared to fluoxetine and placebo in mild to moderate Major Depression (DSM-IV) in a 4-week randomized, double-blind trial**. One hundred and sixty-three outpatients from 15 general practitioner centers received either 900 mg Hypericum LI 160, 20 mg fluoxetine, or placebo daily. Amelioration was measured by the Hamilton and the Montgomery-Asberg Depression scales. Response and remission rates and global ratings by investigators and patients were measured. Adverse event reports, laboratory screening, vital signs, physical exams and ECG were collected. **No significant differences could be observed regarding efficacy measures except for remission rate (Hypericum 24%; fluoxetine 28%; placebo 7%). Hypericum was significantly better tolerated than fluoxetine. Hypericum LI 160 or fluoxetine were not more effective in short-term treatment in mild to moderate depression than placebo**". *(Bjerkenstedt L, Edman GV, Alken RG, Mannel M. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci. 2005 Feb;255(1):40-47).*

34 *Behnke K, Jensen GS, Graubaum HJ, Gruenwald J. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. Adv. Ther. 19, 43-52, 2002.*

35 "**The objective of this double-blind, multi-center clinical study was to demonstrate the non-inferiority of hypericum extract versus sertraline in the treatment of moderate depression. (…) The results indicate that hypericum extract STW 3 is not inferior to sertraline and that it is a well-tolerated drug for the treatment of moderate depression**. These favorable effects were achieved with a once-daily dose of 612 mg of hypericum extract given for up to 24 weeks". *(Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry. 2005 Mar;38(2):78-86).*

36 "**Objective: To investigate the efficacy of hypericum extract WS 5570 (St John's wort) compared with paroxetine in patients with moderate to severe major depression**. **Design: Randomised double blind, double dummy, reference controlled, multicentre non-inferiority trial.** Setting: 21 psychiatric primary care practices in Germany. Participants: 251 adult outpatients with acute major depression with total score > or = 22 on the 17 item Hamilton depression scale. **Interventions: 900 mg/day hypericum extract WS 5570 three times a day or 20 mg paroxetine once a day for six weeks. In initial non-responders doses were increased to 1800 mg/day hypericum or 40 mg/day paroxetine after two weeks. Main Outcome Measures: Change in score on Hamilton depression scale from baseline to day 42 (primary outcome). Secondary measures were change in scores on Montgomery-Asberg depression rating scale, clinical global impressions, and Beck depression inventory. Results: The Hamilton depression total score decreased by mean 14.4 (SD 8.8) points, corresponding to 56.6% (SD 34.3%) of the baseline value, in the hypericum group and by 11.4 (SD 8.6) points (44.8% (SD 33.5%) of baseline value) in the paroxetine group (intention to treat analysis; similar results were observed in the per protocol analysis)**. The intention to treat analysis (lower one sided 97.5% confidence limit 1.5 points for the difference hypericum minus paroxetine) and the per protocol analysis (lower confidence limit 0.7 points) showed non-inferiority of hypericum and statistical superiority over paroxetine. The lower limits in both cases exceeded the pre-specified non-inferiority margin of -2.5 points and the superiority margin of 0. The incidence of adverse events was 0.035 and 0.060 events per day of exposure for hypericum and

risultati dell'Iperico nel trattamento nella depressione maggiore sono piuttosto contrastanti e necessitano senza dubbio di ulteriori approfondimenti. Mentre alcuni studi, tra i quali alcuni dei più recenti che confrontano l'Iperico ad altri antidepressivi, rilevano un trend di efficacia per l'estratto anche su pazienti con depressione severa, altri lavori giungono a conclusioni differenti. Uno studio (Hypericum Depression Trial Study Group, 2002) è stato condotto su 340 pazienti con depressione maggiore con un punteggio alla Scala di Hamilton superiore a 20. Essi ricevevano estratto di Iperico (LI 160) alla dose di 900 o 1550 mg/die o sertralina alla dose di 50 o 100 mg/die o un placebo per 2 mesi. Al termine di questo periodo i pazienti responders continuavano la sperimentazione per altre 18 settimane. La valutazione era fatta ricorrendo alla Scala di Hamilton (HAMD) e secondariamente alla Scala Global Clinical Impression (CGI). Al termine della sperimentazione si è sorprendentemente notato che né l'Iperico né la sertralina erano più efficaci del placebo nel ridurre il punteggio della Scala di Hamilton, mentre la sertralina era significativamente migliore del placebo e dell'Iperico nella Scala CGI. Il risultato potrebbe essere in parte dovuto allo scarso livello di sensibilità del trial, ma gli autori concludono che l'iperico non è efficace nel trattamento della depressione maggiore[37]. Giunge invece a conclusioni diverse una metanalisi più recente, che ha valutato l'efficacia e la tollerabilità dell'iperico paragonata a quella dei selective serotonin reuptake inhibitors (SSRI) in pazienti affetti da depressione maggiore. Sono stati inseriti solo gli studi clinici controllati che hanno paragonato l'effetto nella depressione maggiore dell'Iperico a quello degli SSRI, in tutto 13 lavori. La metanalisi indica che l'Iperico è abbastanza simile agli SSRI come efficacia e leggermente superiore ad essi come tollerabilità in pazienti affetti da depressione maggiore[38]. Ad analoghe conclusioni

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paroxetine, respectively. Conclusions: **In the treatment of moderate to severe major depression, hypericum extract WS 5570 is at least as effective as paroxetine and is better tolerated.**" *(Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005 Mar 5;330(7490):503).*

37 "… **This study fails to support the efficacy of H perforatum in moderately severe major depression. The result may be due to low assay sensitivity of the trial**, but the complete absence of trends suggestive of efficacy for H perforatum is noteworthy." *(Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. JAMA. 2002 Apr 10;287(14):1807-14).*

38 "Hypericum perforatum is a medicinal plant with established antidepressant properties. **The aim of this meta-analysis was to compare the efficacy and tolerability of this antidepressant with selective serotonin reuptake inhibitors (SSRIs) as a group of standard antidepressants**. **For this purpose, Pubmed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies comparing efficacy and/or tolerability of Hypericum with SSRIs in the management of major depressive disorder (MDD).** The search terms were: "Hypericum" or "St. John's wort" and "fluoxetine", "paroxetine", "citalopram", "serteraline", "escitalopram", or "fluvoxamine". **Data were collected from 1966 to 2008 (up to June).** "Clinical response", "remission", "mean reduction in Hamilton Rating Scale for Depression (HAMD) score from baseline", "total adverse events", and "withdrawals due to adverse events" were the key outcomes of interest. **Thirteen randomized placebo controlled clinical trials met our criteria and were included. Comparison of SSRIs with placebo** yielded a significant relative risk (RR) of 1.22 (95% confidence interval: 1.03-1.45, P=0.02) for clinical response (n=4), a non significant RR of 0.96 (95% CI: 0.71-1.29, P=0.76) for remission (n=4), and a significant effect size [weighted mean difference (wmd+)] of 1.33 (95% CI: 1.15-1.51, P<0.0001) for mean reduction in HAMD score from baseline (n=3). **Comparison of Hypericum with SSRIs** yielded a non significant relative risk (RR) of 0.99 (95% confidence interval: 0.91-1.08, P=0.83) for clinical response, a non significant RR of 1.1 (95% CI: 0.90-1.35, P=0.35) for remission, and a non-significant wmd+ of 0.32 (95% CI: -1.28-0.64, P=0.52) for mean reduction in HAMD score from baseline, a non significant RR of 0.85 (95% CI: 0.7-1.04, P=0.11) for any adverse events, and a

giungono gli AA. di una Cochrane review pubblicata nel 2008 che esamina 29 studi randomizzati controllati di buona qualità che hanno interessato 5.489 pazienti, anche se la frequente superiorità dell'Iperico soprattutto negli studi realizzati in Germania complica un po' l'interpretazione dei dati[39]. Una accurata metanalisi pubblicata su The British Journal of Psychiatry[40] ha cercato di stabilire, sulla

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significant RR of 0.53 (95% CI: 0.35-0.82, P=0.004) for withdrawals due to adverse events. **Hypericum does not differ from SSRIs according to efficacy and adverse events in MDD. Lower withdrawal from study due to adverse events by Hypericum is an advantage in management of MDD.**" *(Rahimi R, Nikfar S, Abdollahi M. Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):118-27).*

39 "(…) **A total of 29 trials (5489 patients) including 18 comparisons with placebo and 17 comparisons with synthetic standard antidepressants met the inclusion criteria. Results of placebo-controlled trials showed marked heterogeneity.** In nine larger trials the combined response rate ratio (RR) for hypericum extracts compared with placebo was 1.28 (95% confidence interval (CI), 1.10 to 1.49) and from nine smaller trials was 1.87 (95% CI, 1.22 to 2.87). **Results of trials comparing hypericum extracts and standard antidepressants were statistically homogeneous.** Compared with tri- or tetracyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), respectively, RRs were 1.02 (95% CI, 0.90 to 1.15; 5 trials) and 1.00 (95% CI, 0.90 to 1.11; 12 trials). Both in placebo-controlled trials and in comparisons with standard antidepressants, trials from German-speaking countries reported findings more favourable to hypericum. Patients given hypericum extracts dropped out of trials due to adverse effects less frequently than those given older antidepressants (odds ratio (OR) 0.24; 95% CI, 0.13 to 0.46) or SSRIs (OR 0.53, 95% CI, 0.34-0.83). Authors' conclusions: **The available evidence suggests that the hypericum extracts tested in the included trials a) are superior to placebo in patients with major depression; b) are similarly effective as standard antidepressants; c) and have fewer side effects than standard antidepressants**. The association of country of origin and precision with effects sizes complicates the interpretation." *(Linde K, Berner MM, Kriston L. St John's wort for major depression. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD000448).*

40 "Objectives: **To investigate whether extracts of hypericum are more effective than placebo and as effective as standard antidepressants in the treatment of depressive disorders in adults; and whether they have have less adverse effects than standard antidepressant drugs.** Search Strategy: Trials were searched in computerized databases (Cochrane Collaboration Depression, Anxiety & Neurosis Group Clinical Trials Registers; PubMed); by checking bibliographies of pertinent articles; and by contacting manufacturers and researchers. Selection Criteria: **Trials were included if they: (1) were randomized and double-blind; (2) included patients with depressive disorders; (3) compared extracts of St. John's wort with placebo or standard antidepressants; and (4) included clinical outcomes such as scales assessing depressive symptoms.** Data Collection and Analysis: Information on patients, interventions, outcomes and results was extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of hypericum with placebo and standard antidepressants was the responder rate ratio (responder rate in treatment group/responder rate in control group). The main outcome measure for adverse effects was the number of patients dropping out for adverse effects. Main Results: **A total of 37 trials, including 26 comparisons with placebo and 14 comparisons with synthetic standard antidepressants, met the inclusion criteria. Results of placebo-controlled trials showed marked heterogeneity.** In trials restricted to patients with major depression, the combined response rate ratio (RR) for hypericum extracts compared with placebo from six larger trials was 1.15 (95% confidence interval (CI), 1.02-1.29) and from six smaller trials was 2.06 (95% CI, 1.65 to 2.59). In trials not restricted to patients with major depression, the RR from six larger trials was 1.71 (95% CI, 1.40-2.09) and from five smaller trials was 6.13 (95% CI, 3.63 to 10.38). **Trials comparing hypericum extracts and standard antidepressants were statistically homogeneous.** Compared with selective serotonin reuptake inhibitors (SSRIs) and tri- or tetracyclic antidepressants, respectively, RRs were 0.98 (95% CI, 0.85-1.12; six trials) and 1.03 (95% CI, 0.93-1.14; seven trials). Patients given hypericum extracts dropped out of trials due to adverse effects less frequently than those given older antidepressants (Odds ratio (OR) 0.25; 95% CI, 0.14-0.45); such comparisons were in the same direction, but not statistically significantly different, between hypericum extracts and SSRIs (OR 0.60, 95% CI, 0.31-1.15). Authors' conclusions: Current evidence regarding hypericum extracts is inconsistent and confusing. **In patients who meet criteria for major depression, several recent placebo-controlled trials suggest that the tested hypericum extracts have minimal beneficial effects while other trials suggest that hypericum and standard antidepressants have similar beneficial effects**. As the preparations available on the market might vary considerably in their pharmaceutical quality, the results of this review apply only to the products tested in the included studies." *(Linde K, Mulrow CD, Berner M, Egger M. St John's wort for depression. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD000448).*

base dei migliori lavori pubblicati in letteratura e presenti sui maggiori database biomedici specializzati, se l'estratto di Iperico sia più efficace del placebo e simile come effetto agli antidepressivi di sintesi nel trattamento della sindrome depressiva nell'adulto, con accurata valutazione dei suoi effetti avversi paragonati a quelli dei comuni farmaci antidepressivi sintetici. Dei 68 studi inizialmente recensiti sono stati inclusi nell'analisi 37 studi clinici controllati, di cui 26 versus placebo (3320 pazienti) e 11 versus farmaci (2283 pazienti). I risultati degli studi versus placebo si sono dimostrati marcatamente eterogenei, in parte per le diverse caratteristiche dei pazienti arruolati e in parte per la non uguaglianza dei vari estratti utilizzati. In particolare gli studi su pazienti con depressione maggiore sembrano indicare un'attività dell'Iperico poco superiore al placebo, mentre quelli non limitati alla depressione maggiore mostrano differenze marcate. Differenze nei risultati si osservano anche in base alle dimensioni degli studi. Alcuni recenti studi sembrano inoltre non confermare l'efficacia dell'estratto di Iperico nelle forme più gravi di depressione. Gli studi che hanno paragonato l'Iperico agli antidepressivi di sintesi erano invece assai omogenei e l'analisi ha in particolare evidenziato la significatività statistica dei risultati relativi ai lavori (6 studi) che confrontavano l'Iperico con gli inibitori selettivi del reuptake della serotonina (SSRI). Dall'esame globale delle sperimentazioni che hanno effettuato un confronto parallelo tra l'Iperico ad altri antidepressivi emerge un'efficacia simile, anche se gli studi hanno generalmente utilizzato la dose terapeutica minima del farmaco di sintesi. Riguardo alla tollerabilità, è emerso che i pazienti trattati con Iperico uscivano dagli studi meno di frequente di quelli che ricevevano i farmaci antidepressivi triciclici (Odds ratio (OR) 0.25; 95% CI, 0.14-0.45), mentre la differenza non era statisticamente significativa nei confronti degli SSRI (OR 0.60, 95% CI, 0.31-1.15). La metanalisi conclude che l'estratto di Iperico risulta utile nel trattamento a breve termine della depressione moderata, anche se sono auspicabili altri studi con maggiori caratteristiche di omogeneità (sia per tipologia di pazienti che di estratti) per chiarirne ulteriormente il profilo clinico. Sarebbero inoltre auspicabili anche studi di lunga durata, per potere ricavare informazioni sui rischi di ricaduta e sulla eventuale comparsa di effetti collaterali ritardati[41]. Molto

[41] "The purpose of this report was to evaluate specific depressive symptoms that are most suitable for a therapy with the Ze 117 St. John's wort extract. **We examined the antidepressant efficacy and drug safety of Ze 117 and fluoxetine in a multicentric prospective randomized double-blind parallel group comparison according to generally accepted guidelines such as the Declaration of Helsinki and GCP. We treated outpatients (n = 240; Ze 117: 126; fluoxetine: 114) with mild to moderate depressive episodes (ICD-10: F 32.0, F 32.1; HAMD range: 16-24) with either two tablets St John's wort (Ze 117; 500 mg extract/day) or fluoxetine (20 mg/day) for 6 weeks.** Antidepressant efficacy was evaluated with the validated HAMD psychometric method. A validated analysis of HAMD subscores was made to verify the efficacy for certain depressive symptoms. The main results were: * The HAMD responder rate was 60% in the Ze 117 group compared to 40% in the fluoxetine group (p = 0.005). * Particularly, there was a marked decrease of depressive agitation (pre-post comparison: 46%) and anxiety symptoms (44%) during the therapy with St. John's wort. Depressive obstruction (44%) and sleep disorders (43%) were reduced during the treatment, too. There were no statistically significant differences between the treatment groups. * Adverse events occurred in 28 patients (25%) in the fluoxetine group and in 18 (14%) of the St. John's wort group (p < 0.07). **St. John's wort extract is a clinically effective equivalent to fluoxetine regarding overall depressive symptoms and main symptoms of depressive episodes. An especially interesting overall observation is that Ze 117 is particularly effective in depressive patients suffering from anxiety symptoms**. St. John's wort revealed better safety and tolerability data than fluoxetine**.**" *(Friede M, Henneicke von Zepelin HH, Freudenstein J. Differential therapy of mild to moderate depressive episodes (ICD-10 F 32.0; F 32.1) with St. John's wort. Pharmacopsychiatry. 2001 Jul;34 Suppl 1:S38-41).*

interessante, poi, anche l'impiego della droga nelle depressioni con componente ansiosa[42]. L'*Hypericum perforatum*, infine, si è dimostrato efficace anche nel trattamento delle sindromi ansioso-depressive stagionali[43], disturbi piuttosto comuni e maggiormente frequenti nelle stagioni intermedie (primavera e autunno)[44].

Coadiuvante nella disassuefazione dall'abuso di sostanze. L'estratto di *Hypericum perforatum*, come del resto altri antidepressivi come p.e. la fluoxetina[45], ha dimostrato la capacità di ridurre il craving e l'intake di alcool. L'effetto è stato confermato sperimentalmente in ratti geneticamente alcool-preferenti. La somministrazione per bocca di estratto secco di Iperico allo 0,2% in ipericina e al 4,5% in iperforina riduceva in modo statisticamente significativo il consumo di alcool nei ratti geneticamente alcool preferenti senza causare assuefazione. L'estratto in CO2 (contenente il 24,8% di iperforina) è risultato più efficace dell'estratto metanolico (contenente il 3,8% di iperforina), suggerendo quindi che l'iperforina giochi un ruolo molto importante anche sulla riduzione dell'assunzione di alcool. L'effetto inibitorio sull'assunzione di alcool era inoltre di lunga durata, persistendo per circa 12

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42 "**Long-term safety and the effects of a St. John's wort (SJW) extract Ze 117 (Hypericum perforatum) were evaluated in the treatment of patients with depression. An open multicentre safety study with 440 out-patients suffering from mild to moderate depression according to ICD-10 was conducted. Patients were treated for up to 1 year with 500 mg St. John's wort extract per day (Ze 117)**. Evaluation criteria were safety (adverse event frequency) and influence on depression (HAM-D, CGI). Two hundred and seventeen (49%) patients reported 504 adverse events, 30 (6%) of which were possibly or probably related to the treatment. **Gastrointestinal and skin complaints were the most common events associated with treatment. No age-related difference in the safety of the applied medication was found. The long-term intake of up to 1 year of the study medication did not result in any changes in clinical chemistry and electrocardiogram recordings. Body mass index (BMI) did not change either. Mean HAM-D scores decreased steadily from 20.58 at baseline to 12.07 at week 26 and to 11.18 at week 52. Mean CGI scores decreased from 3.99 to 2.20 at week 26 and 2.19 at week 52. Therefore, St. John's wort extract ZE 117 is a safe and effective way to treat mild to moderate depression over long periods of time, and therefore seems especially suitable for a relapse prevention.**" *(Brattström A. Long-term effects of St. John's wort (Hypericum perforatum) treatment: a 1-year safety study in mild to moderate depression. Phytomedicine. 2009 Apr;16(4):277-83).*

43 "In a randomized, placebo-controlled, double-blind study, 39 patients with depression with somatic symptoms were treated with hypericum extract LI 160. The therapy lasted for 4 weeks; the dosage was 300 mg three times daily… **The results show a significant improvement in the active treatment group at the 5% level as compared to placebo**. Seventy percent of the patients treated with LI 160 were free of symptoms after 4 weeks. Typical symptoms of the depression such as lack of activity, tiredness, fatigue, and disturbed sleep, were especially responsive. In no case were any undesirable side effects observed." *(Hubner WD, Lande S, Podzuweit H. Hypericum treatment of mild depressions with somatic symptoms. J Geriatr Psychiatry Neurol 1994; Suppl 1: S12-4).*

44 "Seasonal affective disorder (SAD) represents a subgroup of major depression with a regular occurrence of symptoms in autumn/winter and full remission in spring/summer… The aim of this controlled, single-blind study was to evaluate if hypericum, a plant extract, could be beneficial in treating SAD patients… We found a significant (MANOVA, $P < .001$) reduction of the Hamilton Depression Scale score in both groups but no significant difference between the two groups. **Our data suggest that pharmacologic treatment with hypericum may be an efficient therapy in patients with seasonal affective disorder.**" *(Martinez B, Kasper S, Ruhrmann S, Moller HJ. Hypericum in the treatment ofseasonal affective disorders. J Geriatr Psychiatry Neurol 1994; Suppl 1: S29-33).*

45 "…Tianeptine and fluoxetine seem to be potent pharmacologically active agents on ethanol withdrawal syndrome in rats. Thus, these anti-depressants may be useful in treatment of ethanol withdrawal syndrome in patients with alcoholism. In addition to serotonergic effects, interactions with nitrergic, glutamatergic, and adenosinergic systems may also provide a significant contribution to the beneficial effects of these drugs on ethanol withdrawal syndrome." *(Uzbay IT. Serotonergic anti-depressants and ethanol withdrawal syndrome: a review. Alcohol Alcohol. 2008 Jan-Feb;43(1):15-24).*

ore[46]. Un altro studio nel ratto ha indagato l'effetto della somministrazione per via intragastrica di un estratto di Iperico ottenuto con CO_2 supercritica sull'introito di alcool dopo un periodo di privazione dall'alcool in ratti alcool preferenti Marchigian-Sardinian. L'estratto veniva somministrato un'ora prima del test tramite sondino naso-gastrico. Per il test dell'autosomministrazione gli animali erano addestrati ad autosomministrarsi etanolo in sessioni giornaliere della durata di 30 minuti. Per il test da deprivazione di alcool i ratti erano deprivati totalmente di alcool per 9 giorni, ma ricevevano acqua e cibo a volontà. In tal caso l'estratto di Iperico veniva dato 1 ora prima della risomministrazione dell'alcool. Si è visto che l'estratto in CO_2 di Iperico alle dosi di 31 o di 125 mg/kg, ma non alla dose di 7 mg/kg, riduceva in modo significativo l'autosomministrazione di alcool e riduceva anche notevolmente l'introito di alcool dopo la sua deprivazione, dimostrando un calo rilevante nel desiderio di alcool. Lo studio conferma che l'estratto in CO_2 di Iperico può rappresentare un potenziale supporto terapeutico nel trattamento dell'alcolismo[47]. In parte ciò può essere dovuto al fatto che la depressione e l'alcolismo hanno in comune alcune analogie neurochimiche, tra cui una diminuita attività cerebrale della serotonina: gli alcolisti sono fortemente carenti di triptofano e ciò potrebbe spiegare sia la depressione sia i disturbi del sonno comuni in questi soggetti, poiché i livelli di serotonina dipendono dalla quantità di triptofano circolante. Inoltre, l'etanolo riduce il trasporto di triptofano al cervello e l'enzima triptofano-pirolasi, considerato l'enzima limitante il catabolismo del triptofano, è più attivo nei ratti durante l'astinenza dall'alcool.

La somministrazione di estratto di Iperico può attenuare anche i sintomi provocati dalla sospensione della nicotina in topi in topi in cui la dipendenza da questa molecola è stata sperimentalmente indotta. D'altra parte, è noto che la nicotina aumenta in vitro il rilascio di 5-HT dai sinaptosomi striatali e che la somministrazione acuta di dosi elevate stimola nel ratto il rilascio di 5-HT dalla corteccia frontale,

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46 *Coskun I, Tayfun Uzbay I, Ozturk N, Ozturk Y. Attenuation of ethanol withdrawal syndrome by extract of Hypericum perforatum in Wistar rats. Fundam Clin Pharmacol. 2006 Oct;20(5):481-8)*

47 "**Extracts of Hypericum perforatum (HPE) attenuate voluntary ethanol intake in different lines of alcohol-preferring rats**. **The present study evaluated the effect of the intragastric (IG) administration of a CO(2) Hypericum perforatum extract (HPCO(2)) on operant ethanol self-administration, as well as on voluntary ethanol intake, after a period of ethanol deprivation in genetically selected Marchigian Sardinian alcohol-preferring rats**. HPCO2 was administered by means of an indwelling IG catheter, 1 h before the tests. For the self-administration experiments, the rats were trained to self-administer 10% (v/v) ethanol in 30-min daily sessions under a fixed ratio 1 schedule of reinforcement. HPCO2 was also tested on 0.2% w/v saccharin self-administration. For the ethanol deprivation experiments, rats that had a previous experience with voluntary ethanol drinking were deprived of ethanol for 9 days, whereas water and food were freely available; HPCO2 was given by IG injection 1 h before the ethanol re-presentation. HPCO2 in doses of 31 or 125 mg/kg but not 7 mg/kg, significantly reduced ethanol self-administration, while it did not modify saccharin self-administration. The same doses of the extract abolished the increased ethanol intake following ethanol deprivation. **These findings provide evidence that HPCO2 markedly reduces the reinforcing properties of ethanol in the self-administration paradigm, as well as the increase of ethanol intake following ethanol deprivation. These findings further support the view that the use of HPE may represent an interesting pharmacological approach in the treatment of alcohol abuse and alcoholism.**" *(Perfumi M, Mattioli L, Forti L, Massi M, Ciccocioppo R. Effect of Hypericum perforatum CO2 extract on the motivational properties of ethanol in alcohol-preferring rats. Alcohol Alcohol 2005 Jul-Aug; 40(4):291-296).*

mentre diminuisce la biosintesi ed i livelli extracellulari del neurotrasmettitore nell'ippocampo[48]. Uno studio ha indagato gli effetti di un estratto di Iperico denominato PH-50 (particolarmente ricco in flavonoidi), sul sistema serotoninergico di topi trattati con dosi consecutive di nicotina in presenza dell'antagonista selettivo del recettore 5-HT_{1A}, WAY 100635. A questo scopo gli animali sono stati trattati per 14 giorni con 4 dosi giornaliere di nicotina al fine di indurre dipendenza. Immediatamente dopo l'ultima dose, due gruppi di topi sono stati trattati per 30 giorni consecutivi con 500 mg/kg per os. di estratto di Iperico o con una soluzione salina, mentre un terzo gruppo è stato cotrattato i.p. per 14 giorni sia con l'estratto che con l'antagonista recettoriale WAY 100635. Tutti gli animali sono stati valutati 24 giorni dopo la sospensione dalla nicotina per l'attività locomotoria e i sintomi da astinenza. I risultati ottenuti hanno dimostrato che l'estratto di *Hypericum perforatum* ha significativamente diminuito i sintomi dell'astinenza rispetto ai controlli, mentre l'antagonista recettoriale WAY 100635 ha inibito gli effetti dell'estratto sui sintomi dell'astinenza. Il contenuto corticale di 5-HT è inoltre risultato significativamente aumentato negli animali trattati con l'estratto di Iperico; tale effetto è stato accompagnato anche da un notevole aumento dell'espressione del recettore 5-HT_{1A}[49].

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[48] "**Hypericum perforatum is used as a natural antidepressant, and other antidepressants have been marketed to aid in smoking cessation. We investigated the effects of an extract of Hypericum perforatum (Ph-50) on withdrawal signs produced by nicotine abstinence in mice**. Methods: Nicotine (2 mg/kg, four injections daily) was administered for 14 days to mice. Different doses of Ph-50 (125-500 mg/kg) were administered orally immediately after the last nicotine injection. In another experiment, Ph-50 (500 mg/kg) was orally administered in combination with nicotine, i) starting from day 8 until the end of the nicotine treatment period, or ii) during nicotine treatment and after nicotine withdrawal, or iii) immediately after the last nicotine injection. On withdrawal from nicotine, all animals were evaluated for locomotor activity and abstinence signs. Results: **The locomotor activity reduction induced by nicotine withdrawal was abolished by Ph-50, which also significantly and dose-dependently reduced the total nicotine abstinence score when injected after nicotine withdrawal. These data show that treatment with Hypericum perforatum attenuates nicotine withdrawal signs in mice.** Further studies are necessary to test the possibility that it may be used for smoking cessation treatment in humans." *(Catania MA, Firenzuoli F, Crupi A, Mannucci C, Caputi AP, Calapai G. Hypericum perforatum attenuates nicotine withdrawal signs in mice. Psychopharmacology (Berl). 2003 Sep;169(2):186-9).*

[49] "**Hypericum** Antidepressants may be effective treatment for smoking cessation and new evidence on relationship between smoking and depression is emerging. **Extracts of the plant Hypericum perforatum possess antidepressant activity in humans and reduce nicotine withdrawal signs in mice**. **Both nicotine and H. perforatum administration elicit changes in serotonin (5-HT) formation in the brain. On this basis, we investigated the possible involvement of 5-HT in the beneficial effects of H. perforatum on nicotine withdrawal signs.** With the aim to induce nicotine dependence, nicotine (2 mg/kg, four intraperitoneal injections daily) was administered for 14 days to mice (NM). Saline (controls, M) or H. perforatum extract (Ph 50, 500 mg/kg) were orally administered immediately after the last nicotine injection for 30 days after nicotine withdrawal. Another group of animals treated with nicotine (14 days) and successively with H. perforatum extract was intraperitoneally co-administered with selective 5-HT receptorial antagonist WAY 100635 (WAY) (1 mg/kg). All animals were evaluated for locomotor activity and abstinence signs, 24 after nicotine withdrawal. Brain 5-HT metabolism was evaluated in the cortex of mice sacrificed 30 days after nicotine withdrawal through evaluation of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) and 5-HIAA/5-HT ratio. After nicotine withdrawal measurement of 5-HT metabolism in the cortex showed a reduction of 5-HT content while animals treated only with Hypericum extract showed a significant reduction of total abstinence score compared to controls. WAY inhibited the reduction of total abstinence score induced by H. perforatum. Moreover, 5-HT1A expression has been evaluated 30 days after nicotine withdrawal. **Our results, show a significant increase of cortical 5-HT content in NM treated with H. perforatum, with a concomitant significant increase of 5-HT1A receptor. So, it is possible to suggest an involvement of 5-HT in beneficial effects of H. perforatum on suffering produced by nicotine withdrawal in dependent mice.**" *(Mannucci C, Pieratti A, Firenzuoli F, Caputi AP, Calapai G. Serotonin mediates beneficial effects of Hypericum perforatum on nicotine withdrawal signs. Phytomedicine. 2007 Oct;14(10):645-51).*

In base a questi dati, il profilo farmacologico dell'estratto di Iperico sembra abbastanza simile a quello del bupropione, il farmaco solitamente adoperato per favorire la disassuefazione dal fumo[50]. Lo studio conferma che l'estratto di Iperico può rappresentare un potenziale supporto terapeutico nel trattamento del tabagismo[51]. Altre recenti ricerche indicano infine che l'estratto di *Hypericum perforatum* potrebbe essere di supporto anche nella terapia della disassuefazione da oppiacei[52,53], suggerendo per la droga un generale ruolo coadiuvante nelle terapie mirate alla disassuefazione dall'abuso di sostanze[54].

Attività sull'apparato cardiovascolare. Il Benigni descrive una azione ipotensiva dell'*Hypericum perforatum* secondaria a vasodilatazione periferica. L'azione ipotensiva-vasodilatatrice dell'*Hypericum perforatum* potrebbe essere dovuta ad una frazione ricca di procianidine che, inibendo le fosfodiesterasi, agirebbero in senso vasodilatatore, riducendo la contrazione delle fibrocellule muscolari lisce di arteria[55].

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50 *Mooney ME, Sofuoglu M. Bupropion for the treatment of nicotine withdrawal and craving. Expert Rev Neurother. 2006 Jul;6(7):965-81.*

51 "Classic synthetic antidepressant drugs, as well as St John's wort extract (SJW), directly inhibit the re-uptake of norepinephrine (NE) and/or serotonin (5-HT) into pre-synaptic axons. With chronic treatment they induce adaptive changes in a number of neurotransmitter receptors in synaptic membranes. **The immediate effects of SJW Ze 117, an extract low in hyperforin content, on the specific dopamine (DA) uptake were studied in rat striatal brain slices and compared with the effects on NE and 5-HT uptake in rat cortical brain slices. Specific DA uptake was inhibited in a dose dependent manner. In contrast to the findings in synaptosomal preparations published so far, the extract showed different inhibitory potencies for the respective transporters. The potencies for the uptake inhibition of NA, DA and 5-HT were 30, 7 and 1, respectively.** The results indicate that the SJW Ze 117 extract interferes in three ways with the individual uptakes of the relevant neurotransmitters that are considered to be causal in the development of depression. **This observation, the concomitant and potent inhibition of DA re-uptake by SJW extract, may additionally provide a rationale for the treatment of nicotine or drug addiction with SJW.**" *(Ruedeberg C, Wiesmann UN, Brattstroem A, Honegger UE. Hypericum perforatum L. (St John's wort) extract Ze 117 inhibits dopamine re-uptake in rat striatal brain slices. An implication for use in smoking cessation treatment? Phytother Res. 2010 Feb;24(2):249-51).*

52 "..It also examined **the effects of Hypericum perforatum L. extracts on the naloxone-induced heroin withdrawal syndrome**. (…) Administration of the heroin to rats for 8 days induced physical withdrawal signs of abdominal constriction, diarrhoea and vocalization on touch after naloxone treatment. Aqueous Hypericum perforatum extracts (20 mg/kg twice daily chronically or as a single acute dose 90 min before naloxone) given orally to the heroin dependent rats attenuated abdominal constrictions both acutely and chronically while the hydroethanol and ethanol extracts were only effective in acutely treated animals. Diarrhoea was ameliorated by the hydroethanol and ethanol extracts following acute or chronic heroin treatment while the aqueous extract failed to show any effect. Vocalization on touch during withdrawal was reduced by all the extracts either chronically or acutely with the exception of chronic treatment with hydroethanol extracts. The findings suggest that Hypericum perforatum is capable of reducing the physical signs of opiate withdrawal." *(Subhan F, Khan N, Sewell RD. Adulterant profile of illicit street heroin and reduction of its precipitated physical dependence withdrawal syndrome by extracts of St John's wort (Hypericum perforatum). Phytother Res. 2009 Apr;23(4):564-71).*

53 *Feily A, Abbasi N. The inhibitory effect of Hypericum perforatum extract on morphine withdrawal syndrome in rat and comparison with clonidine. Phytother Res. 2009 Nov;23(11):1549-52.*

54 *Uzbay TI. Hypericum perforatum and substance dependence: a review. Phytother Res. 2008 May;22(5):578-82.*

55 "Procianidin fractions (PC) were isolated from Hypericum perforatum L. (Guttiferae). Characterization of the main components of each fraction was performed by UV- and mass spectroscopy… A**n inhibition of cellular phosphodiesterase might be involved in the underlying mechanism of action**" *(Melzer R, Fricke U, Holzl J. Institut fur Pharmazeutische Biologie Universitat Marburg, Marburg/Lahn, Fed. Rep. of Germany. Vasoactive properties of procyanidins from Hypericum perforatum L. in*

Altre attività. L'estratto di Iperico si è dimostrato attivo in modelli sperimentali di dolore neuropatico[56,57]. Molto diffuso, p.e. negli stati post-traumatici, post-erpetici, diabetici, carcinomatosi, da artrite reumatoide, si tratta di un dolore molto difficile da curare e da alleviare, ed è provocato dal fatto che a livello del sistema nervoso centrale le fibre nervose trasmettono ai centri del dolore, posti nel cervello, segnali errati. Questa disfunzione dell'attività neurologica provoca, quindi, sensazioni dolorose anche in assenza di un danno reale. L'uso di farmaci anti-infiammatori ed analgesici risulta spesso di scarsa efficacia per cui per molti pazienti si ricorre agli oppiacei, il cui uso comporta però rilevanti effetti collaterali. Ed è proprio per questo che l'attività antinocicettiva dell'*Hypericum perforatum* risulta di particolare interesse.

Studi recenti hanno evidenziato poi una interessante attività protettiva del fitocomplesso di Iperico e dei suoi componenti sulle cellule beta del pancreas, con un effetto preventivo nei confronti del

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isolated porcine coronary arteries. Arzneimittelforschung 1991; 41: 481-3).

56 "Current pharmacological treatments for neuropathic pain have limited efficacy and severe side-effect limitations. St. John's Wort (SJW) is a medicinal plant, mainly used as antidepressant, with a favourable side-effect profile. **We here demonstrate the ability of SJW to relieve neuropathic pain in rat models. The antihyperalgesic profile and mechanism of action of SJW and its main components were studied in two rat models of neuropathic pain: the chronic constriction injury and the repeated administration of oxaliplatin.** SJW, acutely administered at low doses (30-60mgkg(-1) p.o.), reversed mechanical hyperalgesia with a prolonged effect, being effective up to 180min after injection. Further examinations of the SJW main components revealed that hyperforin and hypericin were responsible for the antihyperalgesic properties whereas flavonoids were ineffective. The effect of SJW on the PKC expression and activation was investigated in the periaqueductal grey (PAG) area by immunoblotting experiments. Mechanistic studies showed a robust over-expression and hyperphosphorylation of the PKCgamma (227.0+/-15.0% of control) and PKCvarepsilon (213.9+/-17.0) isoforms in the rat PAG area. **A single oral administration of SJW produced a significant decrease of the PKCgamma (131.8+/-10.0) and PKCvarepsilon (105.2+/-12.0) phosphorylation in the PAG area due to the presence of hypericin. Furthermore, SJW showed a dual mechanism of action since hyperforin antinociception involves an opioid-dependent pathway. Rats undergoing treatment with SJW and purified components did not show any behavioural side effects or signs of altered locomotor activity. Our results indicate SJW as a prolonged antihyperalgesic treatment through inhibition of PKC isoforms and their phosphorylation.**" *(Galeotti N, Vivoli E, Bilia AR, Vincieri FF, Ghelardini C. St. John's Wort reduces neuropathic pain through a hypericin-mediated inhibition of the protein kinase C gamma and varepsilon activity. Biochem Pharmacol. 2010 Jan 4. [Epub ahead of print]).*

57 "**The antinociceptive profile of St. John's Wort (SJW) was investigated in mice in a condition of acute thermal and chemical pain, together with the mechanism that might underlie this effect**. **A dried extract of SJW induced a prolonged antinociception that persisted for 120 minutes after administration.** The thermal antinociception was prevented by naloxone and by the protein kinase C (PKC) activator PMA, whereas the chemical antinociception was prevented by PMA, remaining naloxone insensitive. A chloroform (CHL) and a methanol (MET) fraction, obtained to investigate the involvement of the SJW main components, hyperforin and hypericin/flavonoid, respectively, increased pain threshold with a time course comparable to the dried extract. The CHL antinociception was prevented by naloxone, whereas the MET antinociception was antagonized by PMA. **Purified hyperforin and hypericin showed an antinociceptive efficacy comparable to CHL and MET, respectively**. Conversely, flavonoids were devoid of any effect. The administration of yohimbine and atropine did not modify SJW, CHL and MET antinociception. These results indicate that both CHL and MET fractions mediate the SJW-induced antinociception. In particular, the presence of hypericin was fundamental to induce both thermal and chemical antinociception through the inhibition of the PKC activity, whereas hyperforin selectively produced a thermal opioid antinociception. Perspective: This **article presents evidence of a persistent thermal and chemical antinociception of SJW that is mainly mediated by PKC-inhibiting mechanisms. These findings identify important targets for a longer-acting activation of endogenous pain systems and should potentially help clinicians who seek safe, tolerable, and prolonged treatments for pain relief.**" *(Galeotti N, Vivoli E, Bilia AR, Bergonzi MC, Bartolini A, Ghelardini C. A Prolonged Protein Kinase C-Mediated, Opioid-Related Antinociceptive Effect of St John's Wort in Mice. J Pain. 2010 Feb;11(2):149-159).*

diabete, sia di tipo 1 che di tipo 2[58]. L'azione modulante i livelli intracerebrali di serotonina e di catecolamine e l'azione antiinfiammatoria del fitocomplesso della droga rendono indicato l'impiego dell'Iperico anche nella sindrome premestruale[59]. Sono state infine evidenziate per alcuni dei singoli costituenti del fitocomplesso di *Hypericum perforatum* interessanti proprietà antivirali (ipericina e

[58] "**In both type 1 and type 2 diabetes, increased production of cytokines on autoimmune or metabolic basis is supposed to trigger an inflammatory process leading to dysfunction and death of pancreatic beta-cells**. Therefore, anti-inflammatory pharmacological approaches aimed at blocking cytokine signalling pathways and consequent cytotoxicity in beta-cells are highly advisable. **Based on previous evidence of cytokine antagonistic effects in other cell types, we explored the protective action of Hypericum perforatum (St-John's-wort) extract and its component hyperforin against cytokine-induced functional impairment and apoptosis in the INS-1E beta-cell line, searching for the underlying mechanisms. The results showed that either St-John's-wort extract or hyperforin (at 1-3 microM) prevented cytokine-induced impairment in glucose-stimulated insulin secretion and protected cells against apoptosis in a dose-dependent fashion.** Inducible-NO-synthase expression was also potently hindered by the vegetal compounds. Interestingly, cytokine-induced activations of the signal-transducer-and-activator-of-transcription-1 (STAT-1) and the nuclear-factor-kappaB (NF-kappaB) were both down-regulated by SJW extract or HPF (range 0.5-5 microM) when evaluated by electrophoretic-mobility-shift-assay. Other transcription factors (CBF-1, SP-1) were unaffected. **Components of SJW extract other than HPF were much less effective in down-regulating cytokine signalling. Significantly, inhibition of cytokine-elicited STAT-1 and NF-kappaB activation was confirmed in isolated rat and human islets incubated in the presence of these vegetal compounds. In conclusion, St-John's-wort extract and hyperforin are non-peptidyl compounds which, at low concentrations, target key mechanisms of cytokine-induced beta-cell injury, thereby improving beta-cell function and survival. Thus, they are potentially valuable for the prevention or limitation of beta-cell loss in diabetes.**" *(Menegazzi M, Novelli M, Beffy P, D'Aleo V, Tedeschi E, Lupi R, Zoratti E, Marchetti P, Suzuki H, Masiello P. Protective effects of St. John's wort extract and its component hyperforin against cytokine-induced cytotoxicity in a pancreatic beta-cell line. Int J Biochem Cell Biol. 2008;40(8):1509-21).*

[59] "Premenstrual syndrome (PMS) is a common condition. Some of the most widely prescribed medications are selective serotonin reuptake inhibitors (SSRIs), based on the hypothesized role of serotonin in the production of PMS symptoms. PMS sufferers, especially those experiencing mild to moderate symptoms, are often reluctant to take this form of medication and instead buy over-the-counter preparations to treat their symptoms, for which the evidence base with regard to efficacy is limited. **Hypericum perforatum (St John's wort) influences the serotonergic system. As such, this widely available herbal remedy deserves attention as a PMS treatment. To investigate the effectiveness of Hypericum perforatum on symptoms of PMS. This randomized, double-blind, placebo-controlled, crossover study was conducted between November 2005 and June 2007. Institute of Psychological Sciences, University of Leeds, Leeds, UK. 36 women aged 18-45 years with regular menstrual cycles (25-35 days), who were prospectively diagnosed with mild PMS.** Women who remained eligible after three screening cycles (n = 36) underwent a two-cycle placebo run-in phase. They were then randomly assigned to receive Hypericum perforatum tablets 900 mg/day (standardized to 0.18% hypericin; 3.38% hyperforin) or identical placebo tablets for two menstrual cycles. After a placebo-treated washout cycle, the women crossed over to receive placebo or Hypericum perforatum for two additional cycles. Symptoms were rated daily throughout the trial using the Daily Symptom Report. Secondary outcome measures were the State Anxiety Inventory, Beck Depression Inventory, Aggression Questionnaire and Barratt Impulsiveness Scale. Plasma hormone (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol, progesterone, prolactin and testosterone) and cytokine (interleukin [IL]-1beta, IL-6, IL-8, interferon [IFN]-gamma and tumour necrosis factor [TNF]-alpha) levels were measured in the follicular and luteal phases during Hypericum perforatum and placebo treatment. Hypericum perforatum was statistically superior to placebo in improving physical and behavioural symptoms of PMS ($p < 0.05$). There were no significant effects of Hypericum perforatum compared with placebo treatment for mood- and pain-related PMS symptoms ($p > 0.05$). Plasma hormone (FSH, LH, estradiol, progesterone, prolactin and testosterone) and cytokine (IL-1beta, IL-6, IL-8, IFNgamma and TNFalpha) levels, and weekly reports of anxiety, depression, aggression and impulsivity, also did not differ significantly during the Hypericum perforatum and placebo cycles ($p > 0.05$). **Daily treatment with Hypericum perforatum was more effective than placebo treatment for the most common physical and behavioural symptoms associated with PMS. As proinflammatory cytokine levels did not differ significantly between Hypericum perforatum and placebo treatment, these beneficial effects are unlikely to be produced through this mechanism of action alone**. Further work is needed to determine whether pain- and mood-related PMS symptoms benefit from longer treatment duration**.**" *(Canning S, Waterman M, Orsi N, Ayres J, Simpson N, Dye L. The Efficacy of Hypericum perforatum (St John's Wort) for the Treatment of Premenstrual Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. CNS Drugs. 2010 Mar 1;24(3):207-25).*

pseudoipericina), antinfiammatorie e antibatteriche (iperforina, flavonoidi). L'ipericina[60]. è nota per esercitare una attività antivirale su diversi virus, quali l'HIV-1, il citomegalovirus, l'HSV-1, ecc. L'attività deriva sia da un effetto virucida diretto, sia dalla sensibilizzazione dei virus alla luce ultravioletta[61,62]. Alcuni estratti di *Hypericum perforatum* hanno poi mostrato una attività antibatterica su alcuni batteri Gram-positivi, quali *Staphylococcus aureus* e *Bacillus subtilis*[63].

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[60] "Hypericin is a naturally occurring substance found in the common St. John's Wort (Hypericum species) and can also be synthesized from the anthraquinone derivative emodin. As the main component of Hypericum perforatum, it has traditionally been used throughout the history of folk medicine. In the last three decades, hypericin has also become the subject of intensive biochemical research and is proving to be a multifunctional agent in drug and medicinal applications. **Recent studies report antidepressive, antineoplastic, antitumor and antiviral (human immunodeficiency and hepatitis C virus) activities of hypericin**; intriguing information even if confirmation of data is incomplete and mechanisms of these activities still remain largely unexplained. **In other contemporary studies, screening hypericin for inhibitory effects on various pharmaceutically important enzymes such as MAO (monoaminoxidase), PKC (protein kinase C), dopamine-beta-hydroxylase, reverse transcriptase, telomerase and CYP (cytochrome P450), has yielded results supporting therapeutic potential.** Research of hypericin and its effect on GABA-activated (gamma amino butyric acid) currents and NMDA (N-methyl-D-aspartat) receptors also indicate the therapeutic potential of this substance whereby new insights in stroke research (apoplexy) are expected. Also in the relatively newly established fields of medical photochemistry and photobiology, **intensive research reveals hypericin to be a promising novel therapeutic and diagnostic agent in treatment and detection of cancer (photodynamic activation of free radical production).** Hypericin is not new to the research community, but it is achieving a new and promising status as an effective agent in medical diagnostic and therapeutic applications. New, although controversial data, over the recent years dictate further research, re-evaluation and discussion of this substance. Our up-to-date summary of hypericin, its activities and potentials, is aimed to contribute to this process." *(Kubin A, Wierrani F, Burner U, Alth G, Grünberger W. Hypericin--the facts about a controversial agent. Curr Pharm Des. 2005;11(2):233-53).*

[61] *Hudson JB, Lopez-Bazzocchi I, Towers GH. D. Antiviral activities of hypericin. Antiviral Res 1991; 15: 101-12.*

[62] "During the last decades, Photodynamic Therapy (PDT) has been established as a powerful alternative approved by health agencies of several countries for treatment of various malignant and some non-malignant diseases. PDT makes use of the light-induced destruction of target cells by formation of cytotoxic products in the presence of a photosensitizing agent and oxygen. The **light-dependent tumor destructive properties of Hypericin have drawn attention to its promising application as a photosensitizer in the frame of PDT.** Hypericin is a naturally occurring secondary metabolite in plants of the Hypericum genus, with Hypericum perforatum (St. John's wort) as it is a commonly known representative. **This review focuses on the cellular mechanisms of Hypericin-based phototoxicity and provides an outlook for future application of Hypericin as a fluorescing and photosensitizing agent for diagnosis and treatment of cancerous diseases, respectively.**" *(Kiesslich T, Krammer B, Plaetzer K. Cellular mechanisms and prospective applications of hypericin in photodynamic therapy. Curr Med Chem. 2006;13(18):2189-204).*

[63] "St. John's wort (SJW), an over-the-counter antidepressant, contains hypericin, which absorbs light in the UV and visible ranges. **In vivo studies have determined that hypericin is phototoxic to skin and our previous in vitro studies with lens tissues have determined that it is potentially phototoxic to the human lens**. To determine if hypericin might also be phototoxic to the human retina, we exposed human retinal pigment epithelial (hRPE) cells to 10(-7) to 10(-5) M hypericin. Fluorescence emission detected from the cells (lambda(ex) = 488 nm; lambda(em) = 505 nm) confirmed hypericin uptake by human RPE. Neither hypericin exposure alone nor visible light exposure alone reduced cell viability. However when irradiated with 0.7 J cm(-2) of visible light (lambda > 400 nm) there was loss of cell viability as measured by MTS and lactate dehydrogenase assays. The presence of hypericin in irradiated hRPE cells significantly changed the redox equilibrium of glutathione and a decrease in the activity of glutathione reductase. Increased lipid peroxidation as measured by the thiobarbituric acid reactive substances assay correlated to hypericin concentration in hRPE cells and visible light radiation. Thus, ingested SJW is potentially phototoxic to the retina and could contribute to retinal or early macular degeneration." *(Wielgus AR, Chignell CF, Miller DS, Van Houten B, Meyer J, Hu DN, Roberts JE. Phototoxicity in human retinal pigment epithelial cells promoted by hypericin, a component of St. John's wort. Photochem Photobiol. 2007 May-Jun;83(3):706-13).*

Tollerabilità. Gli estratti di Iperico sono ben tollerati. In rari casi può provocare modeste irritazioni gastriche, cefalea e talvolta sensazione di vertigini e confusione mentale, generalmente reversibili con l'interruzione del trattamento. È stato visto che la droga non possiede gli effetti anticolinergici degli antidepressivi triciclici né causa le disfunzioni sessuali associate all'uso degli inibitori selettivi del reuptake della serotonina. Non si sono mai verificate nei pazienti alterazioni delle performances cognitive, né dell'attenzione, della concentrazione o dei tempi di reazione. In base alle attuali specifiche disposizioni del Ministero della Salute, stabilite allo scopo di garantire la massima sicurezza d'impiego degli integratori alimentari a base di *Hypericum perforatum*, l'apporto massimo giornaliero di ipericina deve essere di 0,7 mg ed è inoltre stabilito che il rapporto iperforine/ipericina non sia superiore a 7, comprendendo nella voce "iperforine" la somma dell'iperforina e dell'adiperforina presenti nell'estratto. (Tali disposizioni, esecutive dal 2009, sostituiscono le indicazioni della Circolare N. 600.12/AG45.1/2688 del 20/10/1999).

L'ipericina può causare reazioni cutanee di fotosensibilizzazione, anche se gli studi indicano che gravi reazioni fototossiche sono da temere soltanto in caso di assunzione di alte dosi (circa 20 volte la dose giornaliera raccomandata) e specialmente in individui dalla carnagione molto chiara. Interazioni additive con altri farmaci fotosensibilizzanti (p.e., clorpromazina o tetracicline) sarebbero teoricamente possibili, ma non sono state sinora descritte. Durante la terapia con Iperico si sconsiglia pertanto la prolungata esposizione ai raggi solari o a lampade abbronzanti[64, 65]. Un monitoraggio effettuato negli ultimi 40 anni mostra come la frequenza degli effetti indesiderati sia scesa dal 50% dei casi per gli antidepressivi triciclici all'attuale 20% per i preparati SSRI; per gli estratti di iperico invece l'incidenza degli effetti indesiderati corrisponde, mediamente, a circa il 3%[66]. È stata

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64 "Clinical evidence suggests that administration of Hypericum perforatum (Hp) extracts containing **the photo-activated hypericin compounds may cause fewer skin photosensitization reactions** than administration of pure hypericin. **This study was conducted to determine whether the phototoxicity of hypericin in HaCaT keratinocytes could be attenuated by H. perforatum extracts and constituents.** Two extracts, when supplemented with 20 microM hypericin: (1) an ethanol re-extraction of residue following a chloroform extraction (denoted ethanol(-chloroform)) (3.35 microM hypericin and 124.0 microM total flavonoids); and (2) a chloroform extract (hypericin and flavonoids not detected), showed 25% and 50% ($p<0.0001$) less phototoxicity than 20 microM hypericin alone. Two H. perforatum constituents, when supplemented with 20 microM hypericin: (1) 10 microM chlorogenic acid; and (2) 0.25 microM pyropheophorbide, exhibited 24% ($p<0.05$) and 40% ($p<0.05$) less phototoxicity than 20 microM hypericin alone. The peroxidation of arachidonic acid was assessed as a measure of oxidative damage by photo-activated hypericin, but this parameter of lipid peroxidation was not influenced by the extracts or constituents. However alpha-tocopherol, a known antioxidant also did not influence the amount of lipid peroxidation induced in this system. **These observations indicate that hypericin combined with H. perforatum extracts or constituents may exert less phototoxicity than pure hypericin**, but possibly not through a reduction in arachidonic acid peroxidation." *(Schmitt LA, Liu Y, Murphy PA, Petrich JW, Dixon PM, Birt DF. Reduction in hypericin-induced phototoxicity by Hypericum perforatum extracts and pure compounds. J Photochem Photobiol B. 2006 Nov 1;85(2):118-30).*

65 *Lopez-Bazzocchi I, Hudson JB, Towers GH. Antiviral activity of the photoactive plant pigment hypericin. Photochem Photobiol 1991; 54: 95-8.*

66 "**Observational studies with preparations of St. John's wort have recorded an incidence of adverse events (AE) among those treated of between 1 and 3%. This is some ten times less than with synthetic antidepressants. The most common adverse events (1 per 300000 treated cases) among the spontaneous reports in the official register concern reactions of the skin exposed to light**. Investigations in volunteers have shown that the threshold dose for an increased risk of

recentemente condotta una metanalisi dei dati presenti in letteratura per quanto riguarda gli effetti avversi dell'Iperico. Sono stati valutati 16 studi di post marketing surveillances per un totale di 34804 pazienti. L'incidenza complessiva di eventi avversi era compresa tra lo 0% e il 6% del numero dei pazienti. In particolare, in quattro studi di fitovigilanza molto ben strutturati condotti su un totale di 14245 pazienti si evidenziarono percentuali di effetti indesiderati comprese tra lo 0,1% e il 2,4% ed interruzioni del trattamento tra lo 0,1% e lo 0,9% del numero di pazienti, ovvero circa 10 volte più basse di quelle dei farmaci antidepressivi di ultima generazione. Inoltre, in quasi tutti i casi gli eventi avversi osservati con iperico erano di grado lieve e transitorio (principalmente irritazioni gastrointestinali). Lo studio conclude che la tollerabilità dell'estratto di Iperico è sicuramente buona, mentre va prestata attenzione alle sue interazioni con altri farmaci[67]. Non sono noti studi con estratti di Iperico in soggetti con insufficienza epatica o renale né dati esaustivi relativi all'impiego dell'iperico durante la gravidanza e l'allattamento.

In definitiva, quindi, è corretto affermare che l'estratto di *Hypericum perforatum* mostra, nel trattamento della sindrome depressiva, un rapporto rischio-beneficio significativamente superiore rispetto ai farmaci antidepressivi correntemente utilizzati in terapia. Di particolare rilevo, quindi, l'impiego nelle depressioni sottosoglia, in cui la sintomatologia lieve/moderata non giustifica un trattamento più aggressivo con ben diversi effetti collaterali[68].

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photosensitisation is about 2-4 g/day of a usual commercial extract (equivalent to approximately 5-10 mg of the hypericin that causes the phenomenon). In view of the newly observed side effects and interactions, the following additional restrictions on use appear justified: as with all preparations in this group of indications, hypericum preparations must not be taken at the same time as other antidepressants. If co-medication with coumarin-type anticoagulants is unavoidable, it must only be undertaken provided the physician closely monitors clotting parameters. Co-medication with ciclosporin and indinavir, and for the time being, other protease inhibitors used in anti-HIV treatment, is absolutely contraindicated. Without exception, all preparations of St. John's wort must only be available through pharmacies." *(Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. Phytomedicine. 2001 Mar;8(2):152-60).*

67 "The clinical efficacy of some standardized St. John's Wort extracts (SWEs) such as WS((R)) 5570, WS((R)) 5572 or LI 160 in the treatment of mild, moderate and severe major depression has been demonstrated in 38 controlled clinical trials and two recent meta-analyses. **Sixteen post-marketing surveillance studies with such preparations, based on a total of 34,804 patients, recorded an incidence of adverse events (AEs) among patients between 0% and 6%. Of these studies, the four large-scale surveillance studies with a total of 14,245 patients recorded a rate of AEs ranging from 0.1% to 2.4% and a drop-out rate due to AEs of 0.1-0.9%. This is at least ten-fold lower than that recorded with synthetic antidepressants.** AEs associated with SWE treatment were mild and transient in nearly all cases. As with synthetic antidepressants, pharmacokinetic interactions may occur occasionally as a result of activity changes of drug-metabolising and drug-transporting proteins, especially CYP 3A4 and P-gp. Risks to the patient are not caused by SWE but by drugs with a narrow therapeutic range. Consequently, SWE preparations should not be taken concurrently with other antidepressants, with coumarin-type anticoagulants, the immunosuppressants cyclosporine and tacrolimus, protease and reverse transcriptase inhibitors used in anti-HIV treatment or with certain antineoplastic agents. However, such cases are extremely rare and, with medical supervision, easily avoided. **In conclusion, the safety of SWE must be considered more favourable than that of synthetic antidepressants**." *(Schulz V. Safety of St. John's Wort extract compared to synthetic antidepressants. Phytomedicine. 2006 Feb;13(3):199-204).*

68 "**Subthreshold depressive disturbances and depressive episodes of mild severity are frequently associated with disability and socioeconomic burden, and often show an increase in symptomatology over time if untreated. Thus, there is an urgent need for antidepressant active compounds that are more readily available than those that must be obtained by prescription**. To get an impression of the efficacy of the widely used phytopharmaceutical St. John's wort, the antidepressant efficacy in mild depressive disorders was compared with that of the standard antidepressant fluoxetine.

Interazioni farmacologiche. La maggior parte delle interazioni tra iperico e farmaci è dovuta all'induzione degli isoenzimi epatici del Citocromo P450 (soprattutto CYP3A4, ma anche CYP2C9 e CYP2D6) e dell'espressione di una proteina di trasporto localizzata nella mucosa dell'intestino tenue, la glicoproteina-P, entrambi coinvolti nel metabolismo di molti farmaci. Si tratta quindi di interazioni su base farmacocinetica. Come tutti gli induttori enzimatici, l'Iperico tende ad accelerare l'eliminazione dei farmaci che vengono solitamente metabolizzati dal sistema del citocromo. Pertanto la co-sommistrazione dell'Iperico con questi farmaci può determinare una riduzione della loro concentrazione plasmatica (e quindi dell'emivita) con possibile diminuzione o perdita dell'effetto terapeutico atteso. Per contro, sospendendo l'assunzione dell'Iperico si potrebbe verificare l'effetto opposto, cioè un aumento della concentrazione nel sangue del farmaco interagente che potrebbe raggiungere livelli tossici se si tratta di un farmaco con basso indice terapeutico[69]. I farmaci per i quali esistono segnalazioni di interazione con iperico sono gli anticoagulanti orali, gli immunosoppressori, l'indinavir e in generale gli inibitori della proteasi e gli inibitori non nucleosidici della trascrittasi inversa per l'infezione da HIV, la digossina, l'irinotecan (citostatico), i contraccettivi orali (estroprogestinici) e la teofillina[70].

The present overview includes controlled trials of fluoxetine in depression with a mean initial score on the Hamilton Rating Scale for Depression (HAM-D) < or =24, which were compared to the respective studies on St. John's wort. The mean HAM-D reduction of all St. John's wort studies was 10.2 (52.9%), and the respective figures for fluoxetine were 12.5 points and 55.5%. Thus, no relevant efficacy difference between the groups of investigations was found based on the studies included. The most important restrictions of this overview are no meta-analysis was performed, the studies were performed with heterogeneous methodological standards, and the St. John's wort extracts used were very different. However, **St. John's wort might be a treatment option to reduce symptoms in patients not suffering from full-blown depressive disorder**." *(Volz HP, Laux P. Potential treatment for subthreshold and mild depression: a comparison of St. John's wort extracts and fluoxetine. Compr Psychiatry. 2000 Mar-Apr;41(2 Suppl 1):133-7).*

69 "We have reviewed the literature to determine the possible interactions between seven popular herbal medicines (ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and conventional drugs. Literature searches were performed using MEDLINE, Cochrane Library and EMBASE and we identified 128 case reports or case series, and 80 clinical trials. **Clinical trials indicate that St John's wort (Hypericum perforatum), via cytochrome P450 (CYP) and/or P-glycoprotein induction, reduces the plasma concentrations (and/or increases the clearance) of alprazolam, amitriptyline, atorvastatin, chlorzoxazone, ciclosporin, debrisoquine, digoxin, erythromycin, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, ivabradine, mephenytoin, methadone, midazolam, nifedipine, omeprazole, oral contraceptives, quazepam, simvastatin, tacrolimus, talinolol, verapamil, voriconazole and warfarin**. Case reports or case series suggest interactions of St John's wort with adrenergic vasopressors, anaesthetics, bupropion, buspirone, ciclosporin, eletriptan, loperamide, nefazodone, nevirapine, oral contraceptives, paroxetine, phenprocoumon, prednisone, sertraline, tacrolimus, theophylline, tibolone, tryptophan, venlafaxine and warfarin. (…)" *(Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs. 2009;69(13):1777-98).*

70 "St. John's wort (Hypericum perforatum, SJW) is one of the most commonly used herbal antidepressants for the treatment of minor to moderate depression. **A major safety concern about SJW is its ability to alter the pharmacokinetics and/or clinical response of a variety of clinically important drugs that have distinctive chemical structure, mechanism of action and metabolic pathways**. This review highlights and updates the knowledge on clinical interactions of prescribed drugs with SJW and the implication in drug development. **A number of clinically significant interactions of SJW have been identified with conventional drugs, including anticancer agents (imatinib and irinotecan), anti-HIV agents (e.g. indinavir, lamivudine and nevirapine), anti-inflammatory agents (e.g. ibuprofen and fexofenadine), antimicrobial agents (e.g. erythromycin and voriconazole), cardiovascular drugs (e.g. digoxin, ivabradine, warfarin, verapamil, nifedipine and talinolol), central nervous system agents (e.g. amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, and sertraline),**

La sostanza principalmente responsabile delle interazioni farmacologiche degli estratti di Iperico è l'iperforina, che interferisce sulla produzione degli enzimi metabolici. È stato infatti dimostrato che l'iperforina si lega al recettore nucleare del pregnano X (PXR) presente nelle cellule umane, causando un significativo aumento dell'espressione del gene che codifica per il CYP3A4. Questa attività, non osservabile *in vitro*, tende ad incrementare la disponibilità del CYP3A4 con conseguente aumento del metabolismo dei farmaci che ne sono substrato[71]. L'effetto è dose-dipendente[72]. Anche per quanto riguarda l'alterazione del sistema di trasporto p-glicoproteico (PGP), l'iperforina sembra essere la sostanza maggiormente coinvolta e, in maniera minore, alcuni flavonoidi. In effetti, estratti a basso contenuto di iperforina sembrano non manifestare significative interazioni farmacologiche[73].

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hypoglycaemic agents (e.g. tolbutamide and gliclazide), immuno-modulating agents (e.g. cyclosporine and tacrolimus), oral contraceptives, proton pump inhibitor (e.g. omeprazole), respiratory system agent (e.g. theophylline), statins (e.g. atorvastatin and pravastatin). Both pharmacokinetic and pharmacodynamic components may play a role in the interactions of drugs with SJW. **For pharmacokinetic changes of drugs by SJW, induction of cytochrome P450s (e.g. CYP2C9 and 3A4) and P-glycoprotein (P-gp) are considered the major mechanism. Thus, it is not a surprise that many drugs that interact with SJW are substrates of CYP3A4, CYP2C9 and P-gp.** A comprehensive understanding of clinical drugs that interact with SJW has important implications in drug development. New drugs may be designed to minimize interactions with SJW; and new SJW formulations may be designed to avoid drug interactions. Further clinical and mechanistic studies are warranted to explore the interaction of SJW with other important drugs and the potential clinical impact." *(Di YM, Li CG, Xue CC, Zhou SF. Clinical drugs that interact with St. John's wort and implication in drug development. Curr Pharm Des. 2008;14(17):1723-42).*

71 *Moore LB, Goodwin B, Jones SA, Wisely GB, Serabjit-Singh CJ, Willson TM, Collins JL, Kliewer SA. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. Proc Natl Acad Sci U S A. 2000 Jun 20;97(13):7500-2.*

72 "The nuclear xenobiotic receptor PXR is activated by a wide variety of clinically used drugs and serves as a master regulator of drug metabolism and excretion gene expression in mammals. **St. John's wort is used widely in Europe and the United States to treat depression. This unregulated herbal remedy leads to dangerous drug-drug interactions, however, in patients taking oral contraceptives, antivirals, or immunosuppressants. Such interactions are caused by the activation of the human PXR by hyperforin, the psychoactive agent in St. John's wort. In this study, we show that hyperforin induces the expression of numerous drug metabolism and excretion genes in primary human hepatocytes.** We present the 2.1 A crystal structure of hyperforin in complex with the ligand binding domain of human PXR. Hyperforin induces conformational changes in PXR's ligand binding pocket relative to structures of human PXR elucidated previously and increases the size of the pocket by 250 A(3). We find that the mutation of individual aromatic residues within the ligand binding cavity changes PXR's response to particular ligands. Taken together, these results demonstrate that PXR employs structural flexibility to expand the chemical space it samples and that the mutation of specific residues within the ligand binding pocket of PXR tunes the receptor's response to ligands." *(Watkins RE, Maglich JM, Moore LB, Wisely GB, Noble SM, Davis-Searles PR, Lambert MH, Kliewer SA, Redinbo MR. A crystal structure of human PXR in complex with the St. John's wort compound hyperforin. Biochemistry. 2003 Feb 18;42(6):1430-8).*

73 "St John's wort (Hypericum perforatum) is an herbal remedy that is widely used in the treatment of depression. Recent clinical data have demonstrated that St John's wort extracts interfere with the action of various drugs and possibly also with combined oral contraceptives. Therefore, **we investigated the effects of a St John's wort extract (Ze 117) with low hyperforin content on the pharmacokinetics of ethinylestradiol and 3-ketodesogestrel.** Method: Sixteen healthy female volunteers, who had taken a low-dose oral contraceptive (Lovelle contains 0.02 mg ethinylestradiol + 0.15 mg desogestrel) for at least 3 months, participated in the study. Pharmacokinetic data (AUC, C(max), t(max)) were determined the day before (reference) and after (test) a 14-day period of Ze 117 intake (250 mg twice daily). Results: Before the co-administration of Ze 117 on day 7, the geometric mean (geometric coefficient of variation) for the AUC(0-24) of ethinylestradiol was 152.53 pg.h/ml (87.39%) and after co-administration on day 21 it was 196.57 pg.h/ml (78.14%). The respective values for ketodesogestrel were 36.37 pg.h/ml (34.18%) and 41.12 pg.h/ml (34.36%). The mean of individual ratios (reference-to-test) of log-transformed AUC values (90% confidence interval) were 0.951 (0.915-0.986) for ethinylestradiol and 0.968 (0.944-0.992) for ketodesogestrel indicating a small gain [corrected] in bioavailability, but bioequivalence nevertheless. **These results indicate that the recommended dose of the hypericum extract Ze117, which has a low hyperforin content, does not interact with the pharmacokinetics of the hormonal components of the low-dose oral contraceptive.**" *(Will-Shahab L, Bauer S, Kunter U, Roots I, Brattström A. St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive. Eur J Clin Pharmacol. 2009 Mar;65(3):287-94).*