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Review Article

Hyperforin: A lead for Antidepressants

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Abstract

Depression is a complex but treatable disorder if diagnosed appropriately. However, despite the advances in the understanding of the molecular basis of this disorder and the vast range of medication, psychotherapy and electroconvulsive therapy, very safe and effective drug to treat this disease is still being sought. Several studies suggest that St.John's wort (*Hypericum perforatum* L.) has phloroglucinol derivative, hyperforin, exhibiting antidepressant activity. This bioactive component can be exploited to create a major shift in the safer treatment of depression.

Keywords: *Hypericum perforatum L.*, St. John's wort, Antidepressant, Hyperforin

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Introduction

Depression continues to be a major cause of disability throughout the world affecting about 121 million people worldwide, the 4th leading contributor to the global burden of disease (DALYs) in 2000 and have a huge societal impact[1]. Depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year. It is associated with distress, despair, hopelessness and low energy.

Treatment of depression by safe and effective antidepressants like SSRIs is a major achievement of 20th century psychophar-macology. Global sales of antidepressant now exceed US $ 10 billion annually, making them the only most important group of psychopharmaceuticals, and include some of most widely used prescription drugs (e.g. Fluoxetine; Prozac). Strangely enough in 2005, the FDA adopted a "black box" warning label on all antidepressant medications to alert the public about the potential increased risk of suicidal thoughts or attempts in children and adolescents taking antidepressants (based on controlled clinical trails conducted by FDA in 2004)[2]. However, these conventional antidepressants have some other limitations:

- It is very difficult to prescribe suitable effective antidepressant judiciously, while starting the treatment for a particular patient i.e. may have to switch to a different medication if first one was not working.
- Antidepressants may cause mild side effects in some people.
- Currently available antidepressant requires administration for at least 2-4 weeks to experience full therapeutic effect or delayed time of onset of antidepressant.
- People taking monoamine oxidase inhibitors (MAOIs) must adhere to significant food and medicinal restrictions to avoid potentially serious interactions.
- Certain populations of patient are resistant to current therapies.

These have led to huge demands of safer and effective antidepressant that address these limitations, which have led to popularity of ancient herbal medicine St.John's wort and their preparations.

St John's wort: Phytopharmacotherapy of Depression

The ethnopharmacological uses and huge prescriptions of St.John's wort (*Hypericum perforatum* L) - best known as 'Nature's Prozac® (fluoxetine)[3] - established this herbal drug as natural antidepressant. All critical analysis on commercial and other information available on sales of herbal medicines in the USA shows that, for the first eight months of 1998, it ranked second to Ginko as the best selling herbal drug, with retail sales valued at over $200 million[4]. In Germany, St John wort is the leading treatment for depression, outselling flouxetine (Prozac®) by a factor of four [5]; some reports estimated 20 times more.

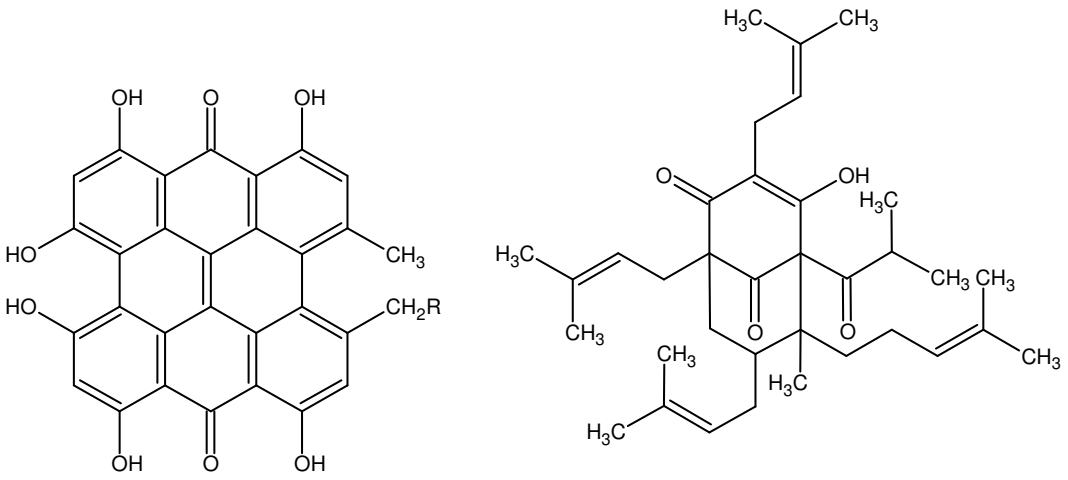
St John's wort consists of the leaves and flowering tops of *Hypericum perforatum* L (Family: *Clusiaceae*), an herbaceous perennial weed commonly found in Asia, Europe and USA[6]. The common name of plant is due to the fact that it flowers around St John's day (24th June)[7]. Paracelsus, a Swiss physician in 1525 discovered its use in psychiatric disorder (neuralgia, anxiety, neurosis and depression) [8]. The plant has long been established in ancient Greece for its other medicinal attributes and has also been used for its antibacterial, anti-viral, diuretics[9], antitumor[10], anti-inflammatory, healing property in peptic ulcers, skin wound and respiratory diseaes[11-14]. *Hypericum perforatum* L is also used in traditional medicines for its anticonvulsant property[15]. The plant has also been employed as an antihelmentic emmenagogue. An oil known as St John's wort oil (*Oleum hyperici*) is prepared by infusing the fresh flowers in

olive oil; used externally in wounds, sores, ulcers, swelling and rheumatism and lumbago[16]. An ointment for use as hair-restorer has been prepared from aqueous extracts of the plant[17]. Leaves of the plants are widely used for diarrhoea, piles, uterine and rectal prolapse. The decoction is reported to treat bleeding. In domestic milch animals, the plant is reported to affect adversely the quantity and flavour of milk[18.] The phytochemical analysis and biological activity data suggested a possible use of *Hypericum perforatum* L extracts in the alimentary, cosmetics, and pharmaceutical fields[19].

Phytochemistry of Hypericum

The phytochemistry of Hypericum has engaged the attention of many scientists due to its wide variety of constituent with biological activity. It contains anthraquinone / naphthadianthrones (principally hypercin and pseudohypercin), prenylated phloroglucinol derivatives (hyperforin, 2.0 - 4.5%, principal lipophilic compound of hydro-alcoholic extracts, phloroglucinol skeleton with lipophlic isoprene chains), flavonoids (such as kaempferol, luteolin and quercetin), and volatile oil (up to 0.35%, saturated hydrocarbon). Some amino acids, vitamin C, tannin and carotenoids have also been reported [9] to be present in the plant. The concentration and proportion of different constituents in the plant are closely related to harvesting period, drying process and storage conditions. Hyperforin content has been reported to increase considerably during fruit development; it increases from 2% (flower) to 4.5% (fruit) of dry weight. The crude drug (fruit) harvested at the beginning of ripening is a better source for extraction of active principle[20].

Out of all components hypercin and hyperforin (figure 1) were more interestingly focused, due to their clinical significance. However several authors have reported flavonoids such as quercetin as anti-inflammatory[21]. Both hyperforin {(1S,5S, 7S,8R)-4-hydroxy-8-methyl-3,5,7-tris(3 methyl but-2-enyl)-8-(4-methylpent-3-enyl)-1-(2-methylpropanoyl) bicycle [3.3.1] non-3-ene-2,9-dione), $C_{35}H_{52}O_4$ and Hypercin (4,5,7,4', 5',7'-hexahydroxy-2,2'-dimethyl-meso-napht-



Pseudohypercin R=OH

Hypercin R=H

Hyperforin

Figure 1: Chemical structures of hypericin and hyperforin, biologically active constituents of St John'swort

hodianthrone, $C_{30}H_{16}O_8$, a red dye obtained from translucent black dots on the surface of calyx and corolla, generally decompose above 330 °C) were initially thought to have MAO-inhibitory antidepressant property [16,22,23]. Hypercin, a phototoxin has also been found to prevent insects from avoiding phototoxicity[24]. Many synthetic hypercin were also synthesized and subjected to clinical trails for the treatment of AIDS.

Many experimental and clinical studies have confirmed that the antidepressant property of St John's wort is not due to hypercin but hyperforin[9, 25 - 29] because:

- Hypercin shows in-vitro MAO-inhibition only at concentration (EC_{50} >10 mg/ml), higher than those found clinically (in-vivo) [30, 31].
- Acute or chronic treatment with St. John wort extract doesn't alter mouse brain MAO-activity[32].
- Extract devoid of hypercin still retain antidepressant activity [33].

Surprisingly, a study by Kumar *et al,*[34] on Indian variety of *H. perforatum* (standardized for hyperforin) showed no MAO-A and B inhibitory activities. Many recent reviews have brought the hyperforin into much sharper focus.

Stability problem

Recently, many studies have raised the question of instability of *H. perforatum* L formulation, owing to degradation of hyperforin. The compound, hyperforin, is more prone to air oxidation, unstable in light and most organic solvents[33]. One study showed a new degradation product of hyperforin namely, deoxyfurohyperforin A, together with the previously identified furohyperforin, furoadhyperforin, furohyperforin A, pyrano[7,28-b] hyperforin and 3 - methyl - 4, 6 - di (3 - methyl - 2 - butenyl) - 2 - (2 - methyl - 1 -oxopropyl) - 3 - (4 - methyl - 3 - pentenyl) - cyclohexanone[35].

Mechanism of action

The mechanism of action of antidepressant activity of hyperforin is still not clear, though the following hypotheses are supported by many publications:

- Hyperforin was found to be potent uptake inhibitor of 5 - HT, Dopamine (DA), Noradrenaline (NA) GABA and L-glutamate (IC_{50}~50-100 $ngml^{-1}$) in synaptsomal preparation from rat striatum[36].
- Hyperforin induces changes in the rat and human electron encephalogram (EEG) that are typical for selective 5-HT reuptake inhibitor[37, 38.]
- Single 300 mg/kg dose of hypericum extract reaches the plasma concentration in rats (~ 700 nM), sufficient for uptake inhibiton[39].
- Hyperforin increases the extracellular brain concentration of (5-HT, DA, NA and glutamate) in the locus coeruleus [40].

However one publication which indicated that "*Hypericum* does not inhibit brain serotonin uptake for inducing antidepressant-like activity in rats" suggests that a mechanism, other than inhibition of 5 - HT uptake, may be responsible for its antidepressant-like activity [41]. A recent study hows that hyperforin induces sodium influx via Transient Receptor Potential Channel (TRPC) mediated by activation of tyrosine kinase receptors and phospholipase C in PC12 cells. This sodium influx leads to an efficient inhibition of serotonin transporters and to an elevation of synaptic serotonin levels.

So antidepressant activity of hyperforin is mediated through transduction pathways. There are indications that the path of novel drug target for new class of antidepressants through the activation of TRPC channels

(potentially useful for drug discovery purpose)[42].

Although various preclinical studies have revealed that the antidepressant effect is still uncertain, and needs to be proved by further experiments, there is not a shadow of doubt in our mind that lipophylic acyl phloroglucinol derivative hyperforin has potential psychotherapeutic value.

Side effects

Hyperforin has been demonstrated to produce some side effects (Table 1). These include

- Photosensitivity that provokes changes in skin pigmentation when it is exposed to sun.
- Serotonergic syndrome when administered simultaneously with paroxetine, a selective serotonin reuptake inhibitor or in sensitive patients.
- Mania episodes associated with the administration to patients more than 50 year old.
- Acute nephropathy after exposure to sun.
- Hepatic cytochrome P450 pathway activation, producing significantly decreased plasma concentration of drugs and reducing their therapeutic actions.
- Hypericin can induce changes in lens protein from calves that could lead to the formation of cataract in the presence of light.

Future Prospects – Semi-synthetic derivatives of Hyperforin

The ethnopharmacological uses and several findings of St John's Wort, through the centuries, has provided a lead which can be exploited for the development of newer antidepressants having improved efficacy and lesser toxicity. However, various successful attempts have been made to synthesize stable hyperforin derivatives (salts and esters) e.g. its dicyclohexyl ammonium salts (Cervo et al[58])), *o* -(carboxymethyl)-hyperforine (Aristoforin)[59], IDN 5491 (hyperforin-trimethoxy benzoate, a semi-synthetic ester)[60]. IDN 5491 has been evaluated for antidepressant activity by forced swimming test (FST) in rats[61].

The efficacy and lack of toxicity of hyperforin make it an interesting lead for the synthesis of structural analogs. This approach has proved very productive, and has resulted in the production of wide range of very active synthetic products, many of which can be used in formulation, since they are more stable to light and stable for longer time. The first synthetic direction is to modify the phenolic moiety. Other modifications are more substantial and consist of replacing the alkyl side chain by heterocyclic structure: furyl, pyridyl residue that could produce a potential antidepressant.

Conclusion

Though St John's wort (*Hypericum perforatum*) has several side effects (Table 1) and drug interactions (Table 2), the plant has afforded an effective arsenal against depression. Therefore, it is crucial to identify the pharmacological interactions of *Hypericum* with other treatments, in order to assess the tolerability of bioactive compounds and to establish with what extent of safety these extracts can be administered to different group of patients.

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Table 1: Some effects of hyperforin

Biological effects	Mechanism	References
Antitumour effect	Competitive inhibition of cytochrome P450 isoform CYP1A1	43, 44
Proapoptotic effect	Release of cytochrome c from mitochondria	45
Antimetastasic effect	Inhibition of ERK ½ phosphorylation	46
Anti-inflammatory effect	COX-1 and 5-LO inhibition	47
Pro-inflammatory effect	Promotor activation through AP-1 dependent mechanism	48
Antiangiogenic effect	Inhibition of endothelial cell growth	46
Antibacterial effect (Active against multiresistant S.aureus and other gram positive bacteria)	No exact mechanism	49
Other neurological effects i.Modulation of β-amyloid secretion ii.Modification of neural membrane fluidity	Altered proteolytic processing by secretases	29
Wound-healing effect	Increase in the stimulation of fibroblast collagen production and the activation of fibroblast cells	50

Table 2: Drug-drug interactions

Co-medication	Interaction	Possible mechanism	References
Digoxin	Lowering of plasma digoxin	Induction of intestinal P-glycoprotein	51
Oral contraceptives	Bleeding	Hepatic enzyme induction	52
Cyclosporine	Lowering of blood cyclosporin	Hepatic enzyme induction	52
Theophylline	Lowering of plasma theophylline	Hepatic enzyme induction	53
Amitriptyline	Lowering of plasma amitriptyline	Hepatic enzyme induction	53
Sertraline	5-HT syndrome	Synergistic 5-HT uptake inhibition	55
Warfarin	Lowering of plasma Warfarin	Hepatic enzyme induction	56
Indinavir	Lowering of plasma indinavir	Hepatic enzyme induction	57

Despite of drug-drug interactions the drug is considered as one of the safest known psychotherapeutic agent.

References

1. WHO-programmes and projects on Depression. http://www.who.int/mental_health/management/depression/ definition/en/. Accessed: 15 June, 2008.
2. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment, a meta-analysis of randomized controlled trials. J of the American Medical Association. 2007; 297 (15): 1683-1696.

3. Gaster B, Holroyd J. St. John's wort for depression. Arch Intern Med 2000; 160:152-6.
4. Ernst E. Second thought about safety of St.John's wort. Lancet. 1999; 354: 2014-2015.
5. Miller AL. St. John wort (Hypericum perforatum): clinical effects on depression and other conditions. Alt.Med.Rev. 1998; 3: 18-26.
6. McIntyre M. The benefits, adverse events, drug interactions, and safety of St John's wort (*Hypericum perforatum*): the implications with regard to the regulation of herbal medicines. J Alt Compl Med. 2000; 6: 115–124.
7. Carlo GD, Borrelli F, Ernst E and Izzo AA. St John's wort: Prozac from the plant kingdom. Trends Pharmacol Sci 2001; 22:6.
8. Bilia AR, GAllori S, Vincieri F F. St.John's wort and depression:efficacy, sfety and tolerability - an update. Life Sciences. 2002; 70(26): 3077-3096.
9. Mennini T and Gobbi M. The antidepressant mechanism of Hypericum perforatum 2004; 75: 1021-1027.
10. Medina MA et al. Hyperforin: More than an antidepressant bioactive compound? 2006; 79: 105-111.
11. Schwarz JT and Cupp MJ. St.John's wort. In Toxicology and Clinical Pharmacology of Herbal Products (Cupp,M.J.ed.). Totowa Humana Press. 2000; 67-78p.
12. Robbers JE and Tyler VE. Tyler's Herbs of Choice. The therapeutic Use of Phytomedicinals. The Haworth Herbal Press, London, 1999.
13. Nathan PJ. The experimental and clinical pharmacology of St. John's wort (Hypericum perforatum L). Mol Psychiatr. 1999; 4: 333-338.
14. Bombardelli E, Morazzoni P. Hypericum perforatum. Fitoterpia. 1995; 66: 43-68.
15. Hosseinzadeh H, Karimi GR, Rakshanizadeh M. Anticonvulsant effect of *H.perforatum* role of nitric oxide J of Ethnopharmacology. 2005; 98 (1-2): pp-207-208.
16. Shastri B.N. H.Perforatum Linn. Wealth of India, National Institute of Science Communication, CSIR, India, 2001; 5: H-K, 155.
17. Schempp CM, Kirkin V, Simon-Haarhaus B, Kersten A, Kiss J, Termeer CC, Gilb B, Kaufmann T, Borner C, Sleeman JP, Simon JC. Inhibition of tumour cell growth by hyperforin, a novel anticancer drug from St. John's wort that acts by induction of apoptosis. Oncogene. 2002; 21: 1242–1250.
18. Shastri B.N. H.Perforatum Linn. Wealth of India, first supplement series, Raw materials. National Institute of Science Communication, CSIR, India, 2005; 3(D-I): 325-326.
19. Confority F, Satti GA, Tundis R, Bianchi A, Agrimonti C, Sacchetti G, Andreotti E, Menichini F, Poli F. Comparative chemical composition and variability of biological activity of methanolic extracts from *Hypericum perforatum* L. Natural Product Research 2005; 19(3): 295-303.
20. Maisenbacher, P., Kovar. Adhyperforin: A Homologue of Hyperforin from *Hypericum perforatum.* Planta Medica. 1992; 58(3): 291.
21. Tedeschi E, Menegazzi M, Margotto D, Suzuki H, Forstermann U, Kleinert H. Antiinflammatory actions of St.John's wort:Inhibition of human inducible nitric-oxide synthase expression by down-regulating signal transducer and activator of transcription-1 alpha (STAT-1 alpha) activation. J Pharmacol Exper Ther .2003; 307 (1): 254-261.
22. Bystrov N S, Chernov BK, Dobrynin VN, Kolosov MN. The structure of hyperforin. Tetrahedron Lett 1975;. 16 (32): 2791-2794.
23. uzuki O, Katsumata Y, Oya M, Blast S, Wagner H. Inhibition of monoamine oxidase by hypericin. Planta Medica. 1984; 50 (3): 272-274.
24. Guedes RC, Eriksson LA. Theoritical study of hypericin. J Photochem. Photobiol Chem 2005; 172: 293 - 299.
25. Treiber K, Singer A, Henke B, Muller W E. Hyperforin activates nonselective cation channels (NSCCs). Br J Pharmacol. 2005; 145: 75-83.
26. Vitiello B, Shader R I, Parker CB.Hyperforin plasma level as a marker of treatment adherence in the National Institutes of Health Hypericum Depression Trail. J Clin Psychopharmacol. 2005; 25:243-249.
27. Zanoli P. Role of hyperforin in the pharmacological activities of St. John's wort. CNS Drug Rev 2004; 10: 203-218.
28. Roz N, Rehavi M. Hyperforin depletes synaptic vesicles content and induces compartmental redistribution of nerve ending monoamines. Life Sci. 2004; 75: 2841-2850.
29. Eckert GP, Keller JH, Jourdan C. Hyperforin modifies neuronal membrane properties in-vivo. Neurosci Lett. 2004; 367: 139-143.
30. Bladt S, Wagner H. Inhibition of MAO by fractions and constituents of Hypericum extracts. J Geriatric Psychiatr Neurol. 1994; 7 (1): S57-S59.
31. Thiede HM, Walper A. Inhibition of Mao and COMT by Hypericum extracts and hypericin. J Geriatric Psychiatr Neurol. 1994; 7 (1): S54-S56.
32. Yu PH. Effect of Hypericum perforatum extract on serotonin turnover in the mouse brain. Pharmacopsychiatr. 2000; 33: 60-65.
33. Chatterjee SS. Hyperforin as a possible antidepressant component of Hypericum extracts. Life Sci 1998; 6: 499-540.
34. Kumar V, Singh PN, Bhattacharya SK. Neurochemical studies on Indian Hypericum perforatum Linn. Indian J Exp Biol 2001; 39: 334-338.
35. Vajs V, Vugdelija S, Trifunovi S, Karadzic I, Jurani N, Macura S and Milosavljevi S. Further degradation product of hyperforin from *Hypericum*

perforatum (St. John's Wort). Fitoterpia. 2003; 75 (5): 439-444.

36. Muller WE. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of Hypericum extract. Pharmacopsychiatr. 1998; 30 (2): 113-116.
37. Dimpfel W. Effect of methanolic extract and a hyperforin - enriched CO_2 extract of St. John's wort (Hypericum Perforatum) on intracerebral field potentials in the freely moving rats. Pharmacopsychiatr. 1998; 31 (1): 30-35.
38. Schellenberg R. Pharmacodynmic effects of two different Hypericum extracts in healthy volunteers measured by quantitative EEG. Pharmaco-psychiatr 1998; 31 (1): 44-53.
39. Biber A. Oral bioavailability of hypericum extracts in rats and human volunteers. Pharmacopsychiatr. 1998; 31 (1): 36-43.
40. Kaehler ST. Hyperforin enhances the extracellular concentration of catecholamines, serotonin and glutamate in the rat locus coeruleus. Neurosci.Lett. 1999; 262: 199-202.
41. Gobbi M and Mennini T. Is St.John's wort a "Prozac-like' herbal antidepressant? TIPS. 2001; 22: 557-559.
42. Treiber K, Singer A, Henke B and Muller WE. Hyperforin activates nonselective cation channels (NSCCs). Br J Pharmacol. 2005; 145 (1): 75-83.
43. 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. Proceedings Nation Acad Sci USA. 2000; 97 (13): 7500-7502.
44. Shay NF, Banz WJ. Regulation of gene transcription by botanicals: novel regulatory mechanisms.Annual. Rev Nutri 2005; 25: 297-315.
45. Hostanska K, Reichling J, Bommer S, Weber M, Saller R. Hyperforin a constituent of St.John's Wort (Hypericum perforatum L.) extract induces apoptosis by triggering activation of caspases and with hypericin synergistically exerts cytotoxicity towards human malignant cell lines. Eur J Pharm Biopharm. 2003; 56(1): 121-132.
46. Dona M, Dell'Aica I, Pezzato E, Sator L, Calabrese F, Della Barbera M, Donella-DeanaA. Appendino G, Borsarini A, Caniato R, Garbisa S. Hyperforin inhibits cancer invasion and metastasis. Cancer Res 2004; 64 (17): 6225-6232.
47. Albert D, Zundrof I, Dingermann T, Muller WE, Steinhilber D,Werz O. Hyperforin is a dual inhibitor of COX-1 and 5-LOX.Biochem Pharmacol. 2002; 64 (12): 1767-1775.
48. Zhou C, Tabb MM, Sadatrafiei A, Grun F, Sun A, Blumberg B. Hyperforin, the active component of St.John's Wort,induces IL-8 expression in human intestinal epithelial cells via a MAPK-dependent, NF-Kappa B-independent pathway. J Clin Immunol. 2004; 24 (6): 623-636.
49. Schempp CM, Pelz K, Wittmer A, Schopf E, Simon JC. Antibacterial activity of hyperforin from St.John's wort,against multiresistant S.aureus and Gram positive bacteria. Lancet. 1999; 353 (9170): 2129.
50. Oztürk N, Korkmaz S, Oztürk Y. Wound-healing activity of St. John's Wort (*Hypericum perforatum* L.) on chicken embryonic fibroblasts. J Ethnopharmacol 2007; 111(1): 33-39.
51. Johne A, Brockmöler J, Bauer S. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999; 66: 338–45.
52. Bon S, Hartmann K, Kuhn M. *Schweitzer Apothekerzeitung.* 1999; 16: 535–36.
53. Nebel A, Schneider BJ, Baker RK, Kroll DJ. Potential metabolic interaction between St John's Wort and theophylline. Ann Pharmacother. 1999; 33: 502.
54. Gordon JB. SSRIs and St John's wort: possible toxicity? *Am Fam Phys* 1998; 57: 950.
55. Lantz MS, Buchalter E, Giambanco V. St John's Wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatr Neurol 1999; 12: 7–10.
56. Yue QY. Safety of St John's wort (*Hypericum perforatum*). *Lancet* 2000; 355: 576–577.
57. Piscitelli SC. Indinavir concentrations and St John's wort. *Lancet.* 2000; 355: 547–548.
58. Cervo L, Rozio M, Ekalle-Soppo CB, Guiso G, Morrazzoni P, Caccia S..Role of hyperforin in the antidepressant-like activity of Hypericum perforatum extracts. Psychopharmacol (Berl) 2002; 164 (4):423-428.
59. Gartner M, Muller T, Simon JC, Giannis A, Sleeman JP. Aristoforin, A novel stable derivative of hyperforin, is a potent anticancer agent. Chembiochem 2005; 6 (1): 171-177.
60. Bombardelli E, Morazzoni P, Riva A, IDN 5491 (Hyperforin trimethoxybenzoate): a new antidepressive drug. Eur. Neuropsychopharmacol. 2002; 12 (3): 240.
61. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 2002; 23: 238-24.