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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

Md Sarfaraj Hussain*1
Md Zaheen Hasan Ansari2
Muhammad Arif1
1Faculty of Pharmacy, Integral University, Lucknow 226026.
2Department of Pharmaceutical chemistry, Jamia Hamdard, New Delhi 110062.

*For Correspondence:
Tel: +91- 9889902496
E-mail: sarfarajpharma@gmail.com
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. 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 psychopharmacology. 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). 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) - 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. In Germany, St John wort is the leading treatment for depression, outselling flouxetine (Prozac®) by a factor of four; 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. The common name of plant is due to the fact that it flowers around St John’s day (24th June). Paracelsus, a Swiss physician in 1525 discovered its use in psychiatric disorder (neuralgia, anxiety, neurosis and depression). 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, antitumor, anti-inflammatory, healing property in peptic ulcers, skin wound and respiratory diseases. Hypericum perforatum L is also used in traditional medicines for its anticonvulsant property. 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. An ointment for use as hair-restorer has been prepared from aqueous extracts of the plant. 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. The phytochemical analysis and biological activity data suggested a possible use of Hypericum perforatum L extracts in the alimentary, cosmetics, and pharmaceutical fields.

**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 / naphthodianthrones (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 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.

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. Both hyperforin \((1S,5S,7S,8R)-4-hydroxy-8-methyl-3,5,7-tris(3 methy- but-2-etyl)-8-(4-methylpent-3-etyl)-1-(2-methylpentanoyl) 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-
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. Hypercin, a phototoxin has also been found to prevent insects from avoiding phototoxicity. 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 because:

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

Surprisingly, a study by Kumar et al. on the Indian variety of Hypericum 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 Hypericum perforatum L formulation, owing to degradation of hyperforin. The compound, hyperforin, is more prone to air oxidation, unstable in light and most organic solvents. 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.

**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 ng/ml) in synaptosomal preparation from rat striatum.
- Hyperforin induces changes in the rat and human electron encephalogram (EEG) that are typical for selective 5-HT reuptake inhibitor.
- Single 300 mg/kg dose of hypericum extract reaches the plasma concentration in rats (~ 700 nM), sufficient for uptake inhibition.
- Hyperforin increases the extracellular brain concentration of (5-HT, DA, NA and glutamate) in the locus coeruleus.

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. 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...
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

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<td></td>
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<td></td>
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<tr>
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Table 2: Drug-drug interactions

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

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47. Albert D, Zundrof I, Dingermann T, Muller WE, Steinhuber D.Werz O. Hyperforin is a dual inhibitor of COX-1 and 5-LOX.Biochem Pharmacol. 2002; 64 (12): 1767-1775.


