



Review Article

Origin, Synthesis and Various Mechanisms of Hypericin as Antidepressant, Photosensitizer and Antiviral

Muhammad Ahsan Waqar<sup>1</sup>, Tehseen Riaz<sup>1</sup>, Muhammad Zaman<sup>1</sup>, Imtiaz Majeed<sup>1</sup>, Muhammad Nadeem Alvi<sup>1</sup>, Ambreen Ishaque<sup>1</sup>, Naila Tabassam<sup>1</sup>, Tooba Mehboob<sup>1</sup>, Muhammad Waqas<sup>1</sup>, Minahal Munir<sup>1</sup> and Saqiba Tayyab<sup>2</sup>

<sup>1</sup>Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan

<sup>2</sup>Care National Hospital, Riyadh, Kingdom of Saudi Arabia

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\*Corresponding Author:

Muhammad Ahsan Waqar  
Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan  
[ahsanwaqar491@gmail.com](mailto:ahsanwaqar491@gmail.com)

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ABSTRACT

Large number of hypericum species have been found around the globe. One of which is the Hypericin, that is extracted from the *Hypericum perforatum*. This review focuses on the brief history of the hypericin, its various natural and semisynthetic sources, the precise pharmacokinetics of the hypericin as well as describes the detailed actions of hypericin as an antidepressant, antiviral and as a phytotoxic agent. In chemical synthesis, Emodin had been found to be the ultimate likely hypericin precursor. Hypericin is not a newly discovered agent to the community of research, nonetheless it has been accomplishing an innovative and a promising position as a very effective agent in the medical diagnostics as well as in the therapeutic applications. Hypericin had been investigated as a good candidate for the treatment of depression, cancer and also had an efficacy against various viral agents as well. Depression is treated by voltage dependent Ca<sup>2+</sup> influx reduction. Photosensitizing property is due to hemoglobin absorption. Antiviral activity is through the deactivation of enveloped viruses in life cycle of virus. With relatively fewer side effects this agent can be utilized as an alternate of various semisynthetic medications.

INTRODUCTION

Saint John's wort or also known as Hypericum, has been among the nine genera that belongs to family of Clusiaceae Lindl and is extensively found all over the globe. Very huge quantities of the species of Hypericum, that includes *Hypericum perforatum* L., *Hypericum androsaemum* L., *Hypericum perforatum* L., *Hypericum chinense* L. and *Hypericum ascyron* L., had been mostly found in Asia, Europe, North America as well as in North Africa. The hypericin concentration varies depending on the species are mentioned in Table 1[1].

Hypericum species	Hypericin (mg. g-1)
<i>Hypericum perforatum</i>	3.69
<i>Hypericum enshiense</i>	3.00
<i>Hypericum hirsutum</i>	0.43

<i>Hypericum aviculariifolium</i>	2.14
<i>Hypericum lydium</i>	0.18
<i>Hypericum montanum</i>	1.42
<i>Hypericum perforatum</i>	1.06
<i>Hypericum organifolium</i>	1.43
<i>Hypericum pruinaum</i>	0.79
<i>Hypericum tetrapterum</i>	0.84
<i>Hypericum wightianum</i>	0.023
<i>Hypericum montbretii</i>	1.39

**Table 1:** Concentration of Hypericin(mg. g-1)in various Hypericum species  
Hypericin is a drug substance that is obtained from *Hypericum perforatum*(Figure 1), that historically had been mainly used as a medicine. Bucher was the scientist who first revealed that hypericin is an active constituent of the *Hypericum perforatum*, as well as this was then later



retitled as hypericin by Cerny in the 1911 [2]. In 1939, first comprehensive isolation report of the hypericin by the Hypericum perforatum was issued by the Brockmann et al., [3]. In 1942, very first chemical formula of the compound hypericin had been reported by Brockmann et al., [4] that is C<sub>30</sub>H<sub>16</sub>O<sub>8</sub> as well as after 8 years, accurate structure had been published by same author [5].



**Figure 1:** *Hypericum perforatum* (St. John's wort)

Literature had shown that hypericin is seldom mentioned as a derivative of naphthodianthrone as well as in the chemical abstracts as 1, 3, 4, 6, 8, 13-Hexahydroxy-10, 11-dimethylphenanthro [1, 10, 9, 8-opqra] perylene-7, 14-dione. Hypericin having molecular weight of 504, had a color of brownish black powdery form and also had a specific type of bitter taste which had mostly been found in the Hypericum plants [6]. Recent reviews attribute status of the hypericin for the cancer treatment [7] as well as also discusses the relevancy of its physical and chemical properties to the pharmaceutical applications [8, 9]. It had been also originated to be mainly effective as the antiviral drug against human immunodeficiency virus [10], herpes virus [11], novel duck reovirus [12], hepatitis C virus [13] and infectious bronchitis virus [14]. Hypericin had also shown some activity as an antioxidant, antimicrobial agent as well as a good choice for the photodynamic diagnosis [15, 16]. This review aims to summarize the natural sources of hypericin, its synthesis from various compounds, kinetics of hypericin and some recent studies that had been performed to prove its efficacy as an antidepressant, phytotoxic and as an antiviral agent.

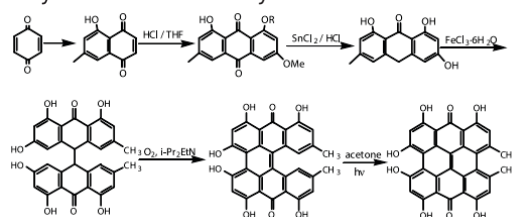
### Sources and Kinetics of Hypericin

Hypericin is a natural occurring bioactive crude substance that could be extracted from the plants, insects as well as from the protozoa [17]. It has been found in superficial layer of Australian Lac insects that belongs to family Coccoidea, as well as found in blue-green ciliate, *Stentor coeruleus*, that is a form of the protozoa. Genus *Hypericum* covers 484 species that are further divided into 36 sub-groups [18]. Out of that the most crucial and recognized specie is the *Hypericum perforatum* that is most usually recognized as St. John's wort. The concentration of hypericin differs and depends on species, as well as topographical locations of *Hypericum* [1, 19] and also on the part of plant. Some recent investigations on kinetic profile of hypericin in humans by using pure hypericin in pure form (0.05 mg/kg body weight)

once a day orally had shown the elimination half-life of about  $33.8 \pm 18.8$  hours, very similar to another study in which the subjects had received 0.1 mg hypericin per kg body weight and had shown elimination half-life of  $36.1 \pm 22.6$  hours. The bioavailability was observed to be 20 % and the steady state had been achieved at two weeks. By daily dosing, no drug accumulation was observed. Any kind of metabolism of hypericin was also not observed in correspondence to mean area under the curve (AUC) determinations that were of 1.5 and 3.1  $\mu\text{g/ml}$  hours respectively [20]. The absorption of hypericin was found in intestine deprived of being metabolized. According to its size of molecule (> 500 Da) and chemical structure, this had been assumed that is excreted in the bile [21]. Moreover, the hypericin had shown a higher non-specific attraction to detergents, lipids and proteins. Kinetic data from a mice in a study had also suggested a distribution half-life of hypericin of about 2 hours as well as an elimination half-life of about 38.5 hr. [22]. These studies had been quite surprisingly similar to the human studies.

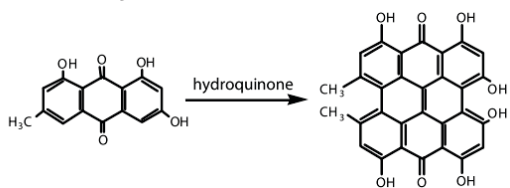
### Synthesis of Hypericin

Hypericin biosynthesis in the *Hypericum* is much further complex than already identified chemically synthetic routes as well as comprises expression of the multiple genes. Generally recognized biosynthetic hypericin pathway could be further divided into two foremost parts, firstly emodin anthrone is formed and then in the second process it is converted to hypericin [23]. Emodin anthrone has been the most probable immediate precursor of hypericin. Many previous investigations had reported that the synthesis of emodin anthrone had followed the pathway of polyketide. Emodin dianthrone could be also formed by condensation reaction of emodin anthrone and the emodin. That afterward then undertakes oxidation to form the protohypericin, and at last protohypericin then is converted to hypericin on irradiation. A scientist Bais et al., [24] had found that the biosynthesis of hypericin is associated to a gene that has been labelled as hyp-1. In 1957, Brockmann, et al., [25] had published very first multistep production of hypericin that was from the chemical synthesis method as shown in Figure 2. Synthesis from this route initiates with reaction of chloral hydrate and 3,5-dimethoxybenzoic acid methyl ester.



**Figure 2:** Hypericin synthesis from 1,4-benzoquinone

Many scientists had now established an even much more simple method to formulate hypericin. In another study, [26, 27] as illustrated in Figure 3, Emodin was transformed to hypericin by the use of hydroquinone as catalyst under nitrogen and the light illumination after 2 weeks.



**Figure 3:** Direct synthesis of hypericin from emodin

### Antidepressant Activity of Hypericin

Depression, a psychiatric condition which had been assessed to affect about 21% of population of the world [28]. Nowadays, four major classes of antidepressant drugs are being prescribed in clinical practice, that includes, selective serotonin reuptake inhibitors (SSRI), norepinephrine-serotonin reuptake inhibitors (NSRI), tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAO). Regrettably, all of these drugs have shown undesirable side effects as well as about 30% of the patients have not respond to these drugs [29]. Consequently, seeking effective and safe antidepressant drugs from the natural and traditional herbs might aid us to discover a novel approach for the treatment of depression. St John's wort preparations are now progressively being used in the depressive disorder treatment [30]. In contradiction of the many rests of the herbal products, effectiveness of St John's wort had been extensively studied in the controlled trials. A new study had reported that some of these trials [31] had shown that St John's wort is much further effective than the placebo for the very short term treatment of moderate to mild depressive conditions. Furthermore, Volz Ž. Ž. In 1997, Stevinson and Ernst in 1999 as well as Maidment Ž. In another study, by use of a preparation of the nerve terminals from cerebral cortex of rat, a new finding was found that the hypericin had effectively inhibits the increased glutamate levels. These investigations had represented the very first investigation of the effect of St. John's wort on endogenous outbreak of glutamate at the presynaptic level. Few early studies had also revealed that antidepressant activity of the hypericin was because of the inhibitory of MAO. However, this activity was originated as in vitro with the extracts concentrations appears to be too high (i.e., > 100 Ag/mL) to be accomplished in vivo [32].

### Photosensitizer Action of Hypericin

Hypericin photosensitizing properties were first known by investigating various reasons of the hypericemia among the animals [33]. Hypericin salts yields solutions with color of wine red in the organic solvents with absorbance  $\lambda_{max}$  of

548 and 591 nm in the ethanol as well as with a typical red fluorescence ( $\lambda_{max}$ : 594 and 642 nm in ethanol), while it tends to form the nonfluorescent high molecular weight aggregates in the solutions that are aqueous [34, 35]. Another site of the intracellular accumulation of hypericin is considered to be lysosomes. Lysosomes works as cell recycling centers which breaks down the molecules which are considered very complex, as well as it damages organelles and components of cell that includes the external pathogens. All of these have been destroyed by enzyme lysosomal hydrolases as well as the products of this collapse and are then dispersed into the cytosol to be either more catabolized as well as recycled into novel components of the cell. Lysosomal integrity of DU145 cells succeeding hypericin sensitization had been evaluated by the monitoring of the action of hexosaminidase enzyme in many other compartments of the cell [36]. These studies had concluded that the damage of lysosomes have not seem to be a key modus operandi of the multifaceted phototoxicity of hypericin. The cells last temporary disruption of lysosomes possibly due to lysosomal enzymes have been disabled that may be either from photodynamic treatment itself, cytoplasm - lysosome lumen pH difference or through the cytosolic inhibitors [37].

### Antiviral Activity of Hypericin

Light induced virucidal activity of hypericin had been observed against numerous types of the viruses including murine cytomegalovirus, herpes, sindbis, equine anemia [38], hepatitis B [39] as well as in human immunodeficiency virus (HIV). Hypericin had been also utilized in treatment of patients suffering with AIDS [40]. It had also shown that therapeutic doses of 0.25 mg/kg when administered to patients two times a week during 2 years, a significant decrease in propagation of HIV infection was observed with comparatively lower adverse effects. Two distinctive properties had been seen for its antiviral activity of as well as for the compounds that are structurally related to hypericin, firstly, they efficiently deactivate the enveloped viruses, nonetheless are very much futile against the non-enveloped viruses [41], and secondly the antiviral activity of Hypericin is strongly triggered and increased by the light. Meruelo et al., have anticipated a mechanism that shows Hypericin inhibits a virus budding as well as maturation at membrane level [42]. Hypericin had also shown to be induce a substantial deactivation of numerous viruses upon contact to the visible light as well as in many cases also observed under the dark conditions. Especially, it had been stated that Hypericin deactivates some variety of the enveloped viruses, although it is very inactive in contrast to the viruses that lacks membranes [43]. A study reported that hypericin is a very effective virucidal agent against the BVDV as well as HIV-1, that acts as a model for the HCV.

Complete inactivation of the 106-tissue culture-infective doses of HIV-1 in entire blood was shown as well as in the diluted packed red cells upon illumination of 50 µg/ml and 20 µg/ml hypericin. BVDV had shown to be much more sensitive to be inactivate by the hypericin than the HIV [44].

## CONCLUSIONS

Number of publications about Hypericin as well as its derived compounds had increased remarkably in the recent decades. This review has focused on the natural and synthetic sources from where hypericin can be obtained and can be utilized for the pharmacological purposes. It could be obtained from several species of *Hypericum* and can be utilized for the pharmacotherapy with minimum side effects than the allopathic medicines. Emodin had been found to be the major precursor for the formation of the Hypericin during the chemical synthesis. Hypericin at specific doses had shown many pharmacological activities such as the antidepressant, photosensitizer and antiviral, yet there are to much more studies that are required to be done to know the exact mechanism of the hypericin for these effects.

## Conflicts of Interest

The authors declare no conflict of interest.

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