Introduction and historical overview

Walter E. Müller

Pharmakologisches Institut für Naturwissenschaftler, Biozentrum Universität Frankfurt, Marie-Curie-Str. 9, 60439 Frankfurt, Germany

The therapeutic properties and advantages of the medicinal herb St. John’s Wort, and preparations derived from it, have been known for more than 2,000 years. However, the specific use of the plant as an antidepressant drug, or as a herbal preparation to treat depressive illness, is relatively recent and has come to the fore only in the last 20 years. St. John’s Wort was first mentioned in the Roman times by Pliny the Elder in the 1st century AD [1]; interestingly it was not to treat melancholia, although the condition was known at that time, but as a “seed of bracing quality which checks diarrhoea and promotes urine and is taken with wine for bladder troubles”. Around the same time, Diascorides, a Roman army doctor born in Greece recommended the imbibition of St. John’s Wort with special liquids “to expel many choleric excrements” [1]. Over 1,000 years later, the famous German physician Paracelsus was one of the first to mention St. John’s Wort as a remedy to treat mental disturbances and also other diseases. He specifically recommended it for three conditions, “wounds, parasites, and phantasmata”, where the latter meant psychoses such as hallucinations and delusion rather than depression [1]. He also mentioned melancholia, but did not specifically suggest St. John’s Wort as treatment. Inspired by Paracelsus, Angelo Sala was probably the first practitioner to specifically recommend St. John’s Wort for depression or melancholia as it was known at that time. In 1630 he wrote (cited from [1]):

“St. John’s Wort has a curious, excellent reputation for the treatment of illnesses of the imagination, which are known by some as phantasmata and by others as mad spirits, and for the treatment of melancholia, anxiety and disturbances of understanding, which sometimes affect highly intelligent people whose primary personality is not melancholic and in whom you do not see persistent melancholic humour. St. John’s Wort cures these disorders as quick as lightning. It takes a day and a night. With the same power it works against the symptoms caused by witches in a way that is superior – as best I can tell – to the effects of any other type of plant or medication, though these may be very highly respected.”

Most importantly, especially considering the present discussion about the relevant active constituents of St. John’s Wort, he suggested that it should best be
given as a tincture made from the fresh petals and leaves by using brandy. He also recommended making the tincture by warming it and to cover the preparation vessel to protect it from daylight. We know today that all these conditions are relevant and that the constituents such as hyperforin and adhyperforin that are not very water soluble are present in goodly amounts. About 200 years later, the German poet-physician J. Kerner also mentioned St. John’s Wort in his writings for the treatment of mood disorders (melancholia). It is quite interesting that for a further century, St. John’s Wort did not receive much more attention, and it was not used as an antidepressant when modern psychiatry first introduced drug-treatment around 1900; at this time drugs such as opium, barbiturates, and other sedatives gained a reputation as antidepressant treatments. Probably the last entry into older history of St. John’s Wort came from the German physician K. Daniel, who not only carried out animal experiments but also described in fine detail his experience with St. John’s Wort extract in the treatment of about 20 depressed patients. Unfortunately, his rather timely publication, which came out just prior to World War II, did not receive much attention in the years following (Daniel, 1939) [2].

The modern history of St. John’s Wort extract probably began in 1984, when Commission E of the former German Federal Health agency, which was determining recommendations for the use of herbal drugs, published a positive monograph about St. John’s Wort, recommending it use for psychoautonomic disturbances, depressed mood, nervousness, and anxiety. According to current standards, this recommendation was based mainly on traditional use and experience, and not on sound scientific data or even clinical studies. However, initiated by this monograph (although this is just an assumption), several smaller companies started to carry out controlled clinical studies (against placebo or against an active comparator, at that time usually a tricyclic antidepressant) in depressed patients. Although usually too small and statistically underpowered according to current standards, these studies gave the first evidence for the clinical usefulness of St. John’s Wort extract in the treatment of depression in Germany, using brands with extract doses of at least a few hundred milligrams per day. These data finally led to the introduction of standardised St. John’s Wort extract brands which allowed a daily dosage of 600–900 mg. Using these new preparations, new controlled clinical studies were performed, which confirmed the clinical efficacy of the herbal drug in mild-to-moderate depressive illness. A first overview about the clinical data and some preliminary pharmacological findings was published in English as a supplement to the Journal of Geriatric Psychiatry and Neurology in October 1994 [3]. These data finally led to an overwhelming acceptance of St. John’s Wort preparations in Germany as an alternative to synthetic antidepressants. In the late 1990s, St. John’s Wort preparations made up as much as 25% of all prescriptions filled out by German doctors for antidepressants. The use and popularity of St. John’s Wort as an antidepressant has also increased in many other countries all over the world [1, 4, 5], but no other country has posted such a high level of acceptance as Germany. This is probably because in most other countries St. John’s Wort