The popularity of ‘natural health’ products or ‘dietary supplements’ containing botanical ingredients continues to rise, according to market research data from the USA. For the year 2016, estimated retail sales of ‘herbal supplements’ totalled more than US$7.4 billion, a substantial increase when compared with 2006 and 2011 figures (US$4.6 billion and US$5.3 billion, respectively).[1] Products containing St John’s wort (Hypericum perforatum L.; Hypericaceae) remain among the most popular herbal products (in the USA, at least): in the 2016 analysis, H. perforatum-containing products were thirty-seventh on the list of top-selling ‘herbal supplements’ in mainstream retail outlets, with total sales of over US$6 million, and were just outside the top 40 products sold from outlets in the natural/wholefoods/lifestyle category.[1]

Alongside sustained consumer interest in H. perforatum, there are indicators that scientific attention on the species also remains strong. For example, a simple literature search in the scientific database Scopus using the phrase ‘(hypericum perforatum)’ yields almost 200 publications for the year 2017.[2] Also, a comprehensive literature review on the chemistry, pharmacology and clinical effects of H. perforatum, published in this journal in 2001, has a citation count of 449 in Scopus; 144 (32%) of these citations have occurred for the period 2013–18 inclusive.[2]

Against this background, this special issue on H. perforatum aims to contribute to the body of knowledge on the species by publishing a collection of original research papers and selected review papers on topics of specific interest related to the medicinal use of the plant. The material included covers topics from the pharmaceutical quality and analysis of H. perforatum preparations, through new insights into the pharmacological effects of H. perforatum extracts and their isolated constituents, to reviews of H. perforatum extracts in clinical practice, including enhancing understanding of H. perforatum drug interactions.

Underpinning this, in research, publishing and literature searching, use of correct nomenclature and search terminology is essential for scientific accuracy and effective retrieval of research publications. However, the importance of this is often overlooked, and the use of imprecise or incorrect plant names is ubiquitous in published literature. The complexities of searching the scientific literature for publications on botanical species, and the importance of botanical nomenclature and taxonomy in this endeavour are tackled by Dauncey et al[3] using H. perforatum as an example. Their position paper illustrates the necessity for researchers to be familiar with the full range of names used to describe a particular species to ensure relevant information is not missed; likewise, to achieve maximum impact when communicating their own research, authors should refer to the current accepted scientific name, scientific synonyms and non-scientific names as far as possible.

The pharmaceutical quality of herbal medicines is an important feature of robust preclinical studies involving these products, and an essential consideration for the safe and effective clinical use of herbal medicines. Several papers in this special issue address the methods for and significance of phytochemical analysis of H. perforatum-based products.

Agapouda et al[4] provide an extensive review of methods used in analysis of H. perforatum-containing products. They consider spectrophotometric quantification convenient, but limited by possible interference from other plant metabolites and difficulties in quantifying individual compounds. TLC, HP-TLC and HPLC-DAD are applied primarily for qualitative analysis of H. perforatum extracts, while LC-MS is used for quantitative analysis. The authors conclude that, considering the wide variety of H. perforatum preparations used
medically, there is no single technique suitable for all applications. HPLC-DAD/UV is suggested as the cornerstone for analysis of routine marker compounds, such as phloroglucinols, naphthodianthrones and flavonoids. For industrial analysis, HP-TLC- and HPLC-based techniques seem most suitable. Modern tools, such as DNA barcoding and NMR metabolomics, have potential and are under development for use within pharmacopoeias, but, at present, DNA barcoding is not acceptable for regulatory quality control. Validation of analytical methods should place particular focus on sample preparation.

Owen et al\[5\] emphasise that the characterisation of both molecular and elemental species in herbal material is important for quality control measures. They describe a systematic method for analysing 11 key metal elements present in H. perforatum material and its preparations, and how sample preparation, inductively coupled plasma–optical emission spectroscopy (ICP-OES) parameters and calibration were optimised.

In a chemometric evaluation, Nigutova et al\[6\] explored the presence of and correlations among several secondary metabolites (including hypericin, pseudohypericin, emodin, hyperforin) in numerous Hypericum species, hairy root cultures and hairy root-derived transgenic plant. A significant positive correlation between hypericins and emodin was observed by both principal component analysis and multidimensional scaling. The authors conclude this indicates the potential of exploiting transgenic plants as sustainable resources of important secondary metabolites with desirable biological activities.

The previously reported pharmacology of H. perforatum extracts as a serotonin-reuptake inhibitor, photodynamic agent and inducer of CYP enzymes is well documented, reflecting the scientific interest in this species and its active phytochemicals. Several papers in this special issue build on this knowledge and report new findings on the pharmacology of H. perforatum. A key feature of herbal medicinal products is that they may have multiple active compounds that interact to yield beneficial effects.\[7\] Verjee et al\[8\] investigated the permeation of hyperforin, one of the active principles of H. perforatum, in Caco-2 cell monolayers, a model system for intestinal permeability in the presence or absence of co-occurring phytochemicals. They found that the extract contains flavonoids and other compounds, such as phenolic acids or proanthocyanidins, which substantially improved the permeation characteristics of hypericin.

A review by Shakya et al\[9\] considered whether there was evidence that the pharmacological properties and active principles of H. perforatum could be augmented in the plant by a process known as elicitation, the use of abiotic and biotic treatments that induce secondary metabolites. Data indicated that extracts obtained from elicitor-treated plant or cell cultures generally possess better bioactivities compared with extracts of control biomass. Compounds induced included hypericins and hyperforin in shoots, and a range of phenolic compounds, flavanols, flavonols, anthocyanins and hypericins in cell culture. Despite encouraging results, elicitation has not yet been exploited due to scale-up difficulties and other issues.

Several papers describe new pharmacological avenues for application of H. perforatum, or its active constituents, in future therapies. For example, the potential for H. perforatum extracts as treatments in sciatic nerve injury (SNI) was explored by Uslusoy et al\[10\] in a rodent model, SNI-induced inflammation, apoptotic, and oxidative damage to muscle, blood and brain was reduced by administration of H. perforatum extract (containing hyperforin 6%). The mechanisms for this appeared to include reductions in lipid peroxidation, raised plasma cytokine concentrations and expression of caspases by H. perforatum.

Similarly, Novelli et al\[11\] investigated the effects of an H. perforatum extract and hyperforin in reducing pancreatic injury in a model of type-1 diabetes in which pancreatic INS-1E cells were injured by exposure to a cytokine mixture. Pre-incubation of these cells with H. perforatum extract and hyperforin initiated a significant STAT-1 down-regulation, and prevented apoptosis and caspase-3 induction. The results suggest the potential for application of H. perforatum in the prevention or treatment of the autoimmune process leading to type-1 diabetes.

Penjewiini et al\[12\] investigated novel formulations of poly-L-lactic acid nanoparticles containing hypericin as experimental photodynamic therapies for cancer. Nanoparticles associate with a small fraction of the whole organelles in HeLa cell populations and these organelles move with higher directed motion. These results should allow better control over targeting of nanotechnology formulations where H. perforatum is used.

Ultimately, it is envisaged that scientific research results in new and/or improved approaches for the prevention and treatment of disease and, increasingly, maintenance of health and wellbeing. H. perforatum-based medicinal products are best known for their effectiveness in reducing symptoms of mild-to-moderately severe depressive disorders.\[13\] However, depression is a serious illness, requiring medical diagnosis, and is unsuitable for self-treatment. In a scoping review of H. perforatum for depression, Forssdike and Pirotta\[14\] find that clinical guidelines for treatment of depression omit H. perforatum, or advise against its use. Also, general practitioners (GPs) rarely recommend H. perforatum to their patients with depressive disorders, and are usually unaware of their patients’ use of H. perforatum as self-treatment. Explanations for this include GPs’ lack of knowledge about H. perforatum, including which specific products to recommend to patients.

General practitioners’ lack of awareness around patients’ use of H. perforatum is of concern, not least because of the
potential for important interactions between *H. perforatum* and certain conventional medicines. Some of these interactions are well documented, but others are understood less clearly. In a new review on this topic, Chrubasik-Hausmann *et al.* consider the impact of the total daily dose of hyperforin provided by different *H. perforatum* products on the likelihood of important drug interactions occurring. They conclude that the risk of interactions is minimised where the total daily dose of hyperforin is less than one milligram, although this does not entirely remove the risk of interactions and could, of course, have implications for the efficacy of the products concerned.

The aim of this special issue was to deepen and extend scientific understanding of the use of *H. perforatum* as medicine and its future potential in this context. At present, despite evidence for the efficacy of certain standardised *H. perforatum* extracts, authorised *H. perforatum* products typically carry ‘low-level’ indications, such as ‘for the relief of symptoms of slightly low mood and mild anxiety’. This is, in part, because ‘light-touch’ regulatory frameworks for herbal medicines usually authorise only products suitable for self-treatment of minor, self-limiting conditions (which depression is not), and because of the recognised difficulties for chemically complex herbal medicinal products in achieving a full marketing authorisation. It remains to be seen whether recent regulatory changes, such as the new ‘assessed listed medicines’ pathway introduced by the Australian Therapeutic Goods Administration as a third possible route for manufacturers to apply to list their products on the Australian Register of Therapeutic Goods, lead to ‘stronger’ indications for *H. perforatum*. This new pathway includes TGA pre-market assessment of evidence of efficacy supporting the proposed indications, and is intended, in part, ‘to allow access to higher level indications than those on the list of permitted indications (i.e. claims relating to unhealthy populations) and indications that make reference to a serious form of disease (restricted representations)’.

In closing, we thank all the authors and peer-reviewers who have contributed to the compilation of this special issue on *Hypericum perforatum L*. We trust that you will find new information and perspectives of interest to you in this collection.

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**References**