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Review

The genus *Rhododendron*: An ethnopharmacological and toxicological review

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ABSTRACT

Ethnopharmacological relevance: The vast genus *Rhododendron* includes species that have been used in traditional medicine for the treatment of inflammatory conditions, pain, gastro-intestinal disorders, common cold, asthma, skin disease, etc. *Rhododendrons* are also well known for their toxicity and some species have been traditionally used as poison.

Aim of the review: The work reviews and analyses the traditional use, biological activities with the corresponding chemical constituents, and toxicological data on *Rhododendron* species. The review aims at characterizing the ethnopharmacology of the genus in relation to its toxicity in order to identify the therapeutic potential of *Rhododendron* species and future directions for research.

Methods: Data regarding *Rhododendron* spp. was collected using electronic databases (SciFinder, PubMed, Google Scholar) and library search for selected peer-reviewed articles. Plant taxonomy was validated by the databases The Plant List, Tropicos, eFloras, Flora Iberica and Flora Europaea (RBGE). Additional information on traditional use and botany was obtained from published books. The review encompasses literature, mainly regarding biological activity and toxicological data, from 1898 to the end of December 2012.

Results: *Rhododendrons* have been used in Asian, North American and European traditional medicine mainly against inflammation, pain, skin ailments, common cold and gastro-intestinal disorders. *In vivo* and *in vitro* testing of plant extracts and isolated compounds determined diverse biological activities including anti-inflammatory, analgesic, anti-microbial, anti-diabetic, insecticidal and cytotoxic activity. *Rhododendron* spp. can cause intoxications in humans following intake of rhododendron honey or medicinal preparations. The toxicity is due to grayanotoxins, diterpenes which activate voltage-gated sodium channels and lead to gastro-intestinal, cardiac and central nervous system symptoms.

Conclusion: *Rhododendron* species are useful traditional remedies for the treatment of inflammation, pain, skin ailments, common cold and gastro-intestinal disorders. Pharmacological data has validated most indications of rhododendrons in ethnomedicine and toxicology studies have confirmed the toxicity observed by traditional use. Ethnopharmacological data point to the therapeutic potential of the genus *Rhododendron* for the treatment of inflammatory conditions and pain and, thus, research should focus on identification of active compounds and related mechanistic studies. Prolonged and high dose intake of traditional formulations containing rhododendrons should be avoided until more in depth toxicity studies become available.

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1. Introduction

Rhododendron is one of the largest genera of vascular plants and covers most of the Northern hemisphere. The first written reference to the species dates as far as 401 B.C. and records the toxicity of rhododendron honey (Gunduz et al., 2007b). Plants of the genus are still known to cause intoxications, mainly due to consumption of contaminated honey. Despite their toxicity, rhododendrons have been used in ancient medical systems such as traditional Chinese and Ayurvedic medicine and also in European and North American folk medicine.

Up to date, the genus provided a large number of chemical compounds of which some indicated pharmacological activity (Qiang et al., 2011). Toxicological studies of *Rhododendron* species addressed clinical data as well as the characterization of toxic constituents (Gunduz et al., 2008; Jansen et al., 2012).

By evaluating indigenous uses, ethnopharmacology provides a base knowledge for further development of medicinal plants and a useful approach for drug discovery (Heinrich and Gibbons, 2001). The genus *Rhododendron* comprises an impressive number of species some of which have been used in traditional medicine. Hence, the purpose of this review is to provide a comprehensive report on the ethnopharmacology of the genus in relation to its toxicity in order to identify its therapeutic potential and future directions for research. This is achieved by a thorough collection and analysis of data related to botany, local and traditional uses, pharmacology and toxicology of *Rhododendron* species.

2. Botany

The genus *Rhododendron* L. (Ericaceae) comprises 8 subgenera with over 850 species (Heywood et al., 2007; Bhattacharyya, 2011). The majority of the species grow in the Himalayan region, South-East Asia and Malesia, with 650 species in China and 155 species endemic to New Guinea (Stevens et al., 2004; Mabberley, 2008). A small number of rhododendrons are distributed throughout North America and Europe. Only two species grow in North-East Australia.

Rhododendrons are evergreen or less often deciduous shrubs or trees (Stevens et al., 2004; Heywood et al., 2007; Bhattacharyya, 2011). The leaves vary in size and are alternate, linear to orbicular with entire margins. The indumentum is glandular, eglandular or with branched hairs. The flowers are generally grouped in raceme or corymb, the inflorescence is rarely axillary and the corolla varies in shape from shallowly lobed to polypetalous. The flowers have 5–20 stamens, anthers with pores or rarely slits, and 5–12-locular ovary. The fruit is a capsule and the seeds are spindle-shaped to ellipsoid or flattened.

3. Traditional uses

Traditional uses of selected *Rhododendron* species (Table 1) point to their importance especially in the treatment of inflammation, pain, common cold symptoms, skin ailments, and gastrointestinal disorders. Some species have also been utilized as insecticides.

In order to cover all published botanical names, a list of synonyms based on the relevant taxonomic literature is provided (Table 2). The list encompasses representatives of the genus that have ethnomedicinal relevance according to the present comprehensive literature review.

3.1. Asia

Most of the ethnomedicinal *Rhododendron* species are employed in Traditional Chinese Medicine for the treatment of arthritis, acute and chronic bronchitis, asthma and pain (Duke and Ayensu, 1985; Tang and Eisenbrand, 1992; Keys, 1993; Kim et al., 1998; Iwata et al., 2004; Li et al., 2011; Wu and Li, 2011; Zhou et al., 2011; Fu et al., 2012). *Rhododendron dauricum* and *Rhododendron molle* are listed in the Chinese Pharmacopoeia and indicated against cough, migraine, swelling and pain associated with injuries from falls, and stubborn tinea (PPRC, 2010).

In Korea, a well-studied species is *Rhododendron brachycarpum*, used in folk medicine for the treatment of diabetes, arthritis, headache and hypertension (Choi et al., 2012). The leaves of *Rhododendron aureum* have been used in Korea and far-Eastern

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