



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### SELENICEREUS GRANDIFLORUS

#### SUMMARY REPORT

1. *Selenicereus grandiflorus* L., synonym *Cactus grandiflorus* or Night blooming cereus, is a plant species of the family *Cactaceae*. The mother tincture of *Selenicereus grandiflorus* is prepared by ethanolic extraction of the fresh young succulent stems and flowers according to the German Homeopathic Pharmacopoeia (HAB, method 3a). In veterinary homeopathy a 1:100 dilution of the mother tincture is used for treatment of food producing animals. The actual degree of extractability of the constituents by homeopathic manufacturing procedures is not known. The use follows the principles of homeopathic therapy where animal are diagnosed on basis of the individual pattern of clinical signs. Depending on the size of animals, usual doses for a single administration are in the range from 1 ml (animals of about 5 kg bw) to 10 ml (animals of about 400 kg bw) for parenteral use. Corresponding doses for oral treatment with tablets or globules contain lower amounts of cactus constituents than the injectable form. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy.

In human homeopathic medicine preparations of *Selenicereus grandiflorus* may be used in all homeopathic dilutions including mother tincture. Fresh or dried overground parts of the plant are also used in traditional human phytotherapy. The dose is for instance 0.6 ml of a fluid extract, up to 10 times daily.

2. The flowers of *Selenicereus grandiflorus* contain betacyanins and flavonolglycosides, the latter approximately amounting to 1.5%. About 8 glycosylated flavonoids have been identified: narcissin (synonym: lycorine or isorhamnetin-3- $\beta$ -rutinoside, 0.05%), cacticin (synonym: isorhamnetin-3- $\beta$ -galactoside, 0.02%), rutoside (synonym: rutin or quercetin-3-rutinoside), hyperoside (synonym: hyperin or quercetin-3- $\beta$ -D-galactopyranoside), kaempferitrin (synonym: kaempferol-3,7-O-dirhamnoside), grandiflorine (synonym: kaempferol-3- $\beta$ -L-arabinoside), isorhamnetin-3-O- $\beta$ -(xylosyl)-rutinoside and isorhamnetin-3-O- $\beta$ -(galactosyl)-rutinoside. The stems appear to contain the same spectrum of flavonoids. Additionally, biogenic amines like tyramine (0.3% in the dry matter), N-methyltyramine and N,N-dimethyltyramine (synonym: hordenine) have also been found in the stems. Further constituents of *Selenicereus grandiflorus* are mucus, fat, wax and resinous glycosides.
3. Some reports on pharmacodynamic properties of *Selenicereus grandiflorus* are available, but the possible mechanism of action remains unclear. The medicinal herb is said to possess a stimulating effect on heart, blood pressure and motor neurons of the spinal cord. As reported from old *in vitro* studies there is some indication of positive inotropic effect (studies with isolated frog heart and papillary muscle probably from guinea pig). This effect may be attributed to plant constituents like tyramine, N-methyltyramine and N,N-dimethyltyramine. In principle, these substances can have a sympathomimetic action with indirect effects on adrenergic receptors exerting only peripheral action. On the other hand, actual concentrations of tyramine and its two derivatives in *Selenicereus grandiflorus* seem to be too low to exert any pharmacological effects. Concerning hordenine, an insignificant increase of heart rate for the duration of 90 seconds has been observed in horses following intravenous injection of 200 mg/animal. However, it has also been reported that after oral administration of 500 mg hordenine to horses no effects on circulation occurred. Antihypertensive and antiarrhythmic activities have been ascribed to the class of flavonoid substances and flavonoids were reported to decrease capillary permeability and fragility.

4. Specific pharmacokinetic information for extracts of *Selenicereus grandiflorus* was not available and data on individual plant constituents was limited. As regards flavonoids, pharmacokinetics may be characterised as follows: Flavonoids are normally considered as poorly absorbable when present as glycosides. Only free hydrolysed flavonoid aglycones are thought to be absorbed to a certain degree. For absorbed flavonoids, there is evidence for methylation, sulphatation and glucuronidation of hydroxyl groups in the liver and excretion into urine and bile. Concerning the tyramines a rather complete oral absorption has been reported. However, since these amines are good substrates of the monoaminoxidases, systemic bioavailability is considered low (about 10%). For hordenine a very short half-life of only 24 minutes has been determined in horses.
5. Data on acute and repeated dose toxicity of *Selenicereus grandiflorus* was not provided. With respect to the single constituents of *Selenicereus* little information of limited value is only available on the flavonoid narcissin (lycorine), which is also classified as alkaloid. The following LD<sub>50</sub> values have been reported for the mouse: 10 700 mg/kg bw orally; 145 mg/kg bw subcutaneously (original study was not available).
6. No studies on reproductive effects including teratogenicity of *Selenicereus grandiflorus* or its constituents have been performed.
7. Specific data on mutagenic activities of *Selenicereus grandiflorus* and constituents thereof were not available. Referring to the flavonoids in general, it may be noted that some substances of this class were found to exert mutagenic effects in *in vitro* assay systems. Most investigations have focused on quercetin, a flavonoid widely distributed in food items, which is the aglycone of hyperoside and rutoside contained in *Selenicereus grandiflorus* and, additionally, the isorhamnetin (synonym: quercetin-3,7'-dimethylether) containing compounds which are structurally related to quercetin.

While tumour inducing effects of quercetin and derivatives have been reported in a few rat studies the majority of *in vivo* experiments have shown that quercetin and related derivatives are not carcinogenic. On the other hand, there is some evidence that flavonoids possess antimutagenic and anticarcinogenic properties. There are no published data indicating genotoxic hazards connected with flavonoids or other constituents present in extracts of *Selenicereus grandiflorus*.

8. No specific studies on immunotoxicity were provided.
9. In humans it is reported that dermal contact of the fresh juice of *Selenicereus grandiflorus* may cause skin irritations with pruritus and pustules. Contact of the juice with the mouth may result in a feeling of burning possibly associated with nausea, vomitus and diarrhoea. However, detailed case reports were not available.
10. It was not possible from the available information to establish a complete pharmacological and toxicological profile including NOELs and an ADI for *Selenicereus grandiflorus* extracts and its constituents. Risk assessment may be based on the following general safety considerations which appear to indicate that none of the constituents of *Selenicereus grandiflorus* gives rise to specific consumer health concerns:
  - Betacyanins in the flowers of *Selenicereus grandiflorus* are normal food constituents, occurring for instance in beetroot red obtained from the roots of *Beta vulgaris var. rubra*. Beetroot red is used as a colouring agent for foodstuffs and cosmetics (E 162).
  - The flavonoids are natural constituents occurring in significant quantity in nearly all animal and human diets. In the Netherlands, the daily intake of 5 different flavonoids (including quercetin, luteolin, kaempferol, apigenin, myricetin including their glycoside derivatives) with the human diet was estimated with 25 mg/day (more than 60% being quercetin). In the USA the estimated total consumption of flavonoids in human diet is about 1g/day. The intake of flavonoids in the diets of the food-producing herbivores certainly far exceeds these figures.

- The biogenic amines tyramine, N-methyltyramine and N,N-dimethyltyramine (i.e. hordenine) may be expected to occur in all plants with capability of metabolic proteolysis. Tyramine is a normal constituent of animal derived food and occurs in the organism of humans as a result of decomposition of the amino acid tyrosine. It is further methylated to N-methyltyramine and N,N-dimethyltyramine. Hordenine for example is contained in sprouting barley and may therefore be expected in products thereof.

### Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- *Selenicereus grandiflorus* is used as a diluted extract not exceeding one part per hundred, prepared according to homeopathic pharmacopoeias,
- major constituents of *Selenicereus grandiflorus* are normal components of human and animal diet,
- *Selenicereus grandiflorus* is used in a small number of individual animals for non-regular treatments, in accordance with the principles of homeopathic therapy,
- the animals are unlikely to be sent for slaughter during or immediately after treatment;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for homeopathic preparations of *Selenicereus grandiflorus* at concentrations not exceeding one part per hundred and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
<i>Selenicereus grandiflorus</i>	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per hundred only.