



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Rosa gallica* L., *Rosa centifolia* L., *Rosa damascena* Mill., flos

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

### Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Rosa gallica</i> L., <i>Rosa centifolia</i> L., <i>Rosa damascena</i> Mill., flos
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal substance or comminuted herbal substance for infusion preparation for oromucosal or cutaneous use.
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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The herbal substance (Rose flower) consists of the dried petals of flowering herb of *Rosa gallica* L., *Rosa centifolia* L. or *Rosa damascena* Mill.

It has been distinguished between white (Flores rosae centifoliae, Flores rosae incarnatae, Flores rosae pallidae, Flos rosae pallidae, Rosae centifoliae petala) and red (Flores rosae gallicae, Flores rosae rubrae, Flos rosae rubrae, Petala rosae rubrae, Rosae gallicae petala) rose flowers (Blaschek *et al.* 2006).

**Rose** is a common name given to the thorny shrubs and climbing vines of the genus *Rosa* in the Rosaceae family. More than 100 *Rosa* species have been recorded throughout the world. Because rose is a popular garden plant, it is virtually impossible to determine the number of currently existing cultivars. The *Flora of Turkey and the East Aegean Islands* identifies 24 *Rosa* species growing in this region of the world.

The French Pharmacopoeia contains 2 monographs:

- *Rosa gallica* (Rose rouge, 1989i),
- *Rosa centifolia* (Rose pâle, 1989ii), also in DAC (2012).

### ***Rosa damascena* Mill.**

*Rosa damascena* Mill. is an erect shrub 1–2 m in height. Flowers of this plant are large, showy and colorful. *Rosa damascena* today are highly cultivated all over the world, including Iran (especially in Kashan), for visual beauty and its scent (Boskabady *et al.* 2006; Blaschek *et al.* 2006).

Synonymes: *Rosa bifera* Pers., *Rosa calendarum* Borkh., *Rosa centifolia bifera* Poirlet, *Rosa gallica* var. *damascena* Voss, *Rosa menstrua* Andr.

### ***Rosa gallica* L.**

The flowers are usually solitary, more rarely in twos and threes, on 2 to 3 cm long thickly glandular pedicels. The calyx is round to pear-shaped and is usually thickly covered with stem glands and gland bristles. The velvety petals are pink to purple, 2 to 3 cm long and wide. The style and stigma form the ovary and that is surrounded by carpels enclosed in the calyx, forming woolly capitula. The ripe, red brown false fruits are 1 to 1.5 cm long.

*Rosa gallica* is a low shrub with extensive runners and above ground reed like shoots, which are erect and branched. They usually grow to between 0.5 to 1 m and are covered with long revolute, or erect thorns and stem glands of different length. The leaves, which are usually pinnate, less frequently trifoliate, have long glandular, dark green above, lighter and bluer below, leaflets. They grow together at the leaf stem that terminate in free tips (Gruenwald *et al.* 2007).

### ***Rosa centifolia* L.**

Synonyms : Rose pâle (PF X), Rose rouge (PF X), Flos rosae (Helv 5), Flores Rosae (EB 6), Red-Rose petal (Blaschek *et al.* 2006).

## Chemical constituents according to existing references

### ***Rosa damascena* Mill.**

*Rosa damascena* Mill. contains carboxylic acid, terpene, myrcene and vitamin C (Boskabady *et al.* 2006, Gennadios 1914).

- Flavonoids

Flavonoids such as kaempferol and quercetin glycosides were detected (quercetin 3-O-galactosid, quercetin 3-O-xyloside kaempferol glycosides). The kaempferol glycosides, along with the kaempferol aglycone, accounted for 80% of the total compounds that were quantified, with kaempferol 3-O-glucoside being the predominant component (Kumar *et al.* 2009)

A high flavonol content of approximately 16 g/kg on a dry weight basis was reported containing rutin, quercitrin, myricetin, quercetin, apigenin, and kaempferol (Kumar *et al.* 2009).

A new flavonoid glycoside, kaempferol-3-O-beta-D-glucopyranosyl(1-->4)-beta-D-xylopyranoside, named roxyloside was isolated from the buds of this plant, along with isoquercitrin, afzelin, and quercetin gentiobioside (Kwon *et al.* 2010). New aurones, damaurones A and B were very recently isolated from the flowers of *Rosa damascena* (Gao *et al.* 2013)

- Catechin, epicatechin,
- Anthocyanins (such as cyanidin-3-O- $\beta$ -glucoside)
- Proanthocyanidins
- Phenolic acids (gallic acid, m-coumaric acid)
- Major carotenoids, such as  $\beta$ -carotene, lycopene, rubixanthin, zeaxanthin and lutein
- Vitamin C

### **Chemical constituents of Rose Oil**

The basic character of rose oil, mostly dependent upon citronellol and geraniol, is further modified by nerol (5 to 11%) and farnesol (0.2 to 1.4%). Their contents are slightly higher in village type distilled oils. Higher farnesol content leads to the establishment of strong floral character and an overall improvement of body-note volume. Nerol not only adds to the rosaceous character but also to its freshness. In those cases where the geraniol content is low, however, the freshness of nerol manifests itself as slightly citrusy. When geraniol content is high; the combination of citronellol, geraniol, farnesol, and nerol results in a strong, sweet, floral, fresh rosaceous character. Other typical constituents of rose oil are geranyl acetate, nonanal, citronellyl formate, citronellyl acetate, eugenol, methyl eugenol, cis-rose oxide,  $\alpha$ -terpineol, phenylethyl alcohol and linalool. Damascenones and some sulfur compounds are among the minor components. Stearoptenes (paraffins) are natural constituents of rose oil (primarily nonadecane) and due to their presence, rose oil solidifies at room temperature and when refrigerated (Can Baser *et al.* 2012).

The chemical composition and physical properties of the rose absolute produced from rose concretes and the extract, showed that rose absolute consists mainly of beta-phenylethyl alcohol, citronellol, geraniol, nerol, eugenol, methyl eugenol, geranyl acetate, benzyl alcohol, nonadecane, nonadecene and farnesol. It was observed that the solid residue contains mainly straight-chain saturated hydrocarbons with high molecular weight (C-15-C-31) and the esters of carboxylic acids and a homologous series between them exists. It was also concluded that the extract obtained by solvent

extraction from the residue of rose flower (*Rosa damascena* Mill.) which was subjected to steam distillation is also a valuable raw material (Ayci *et al.* 2005).

- Herbal preparation(s)

Comminuted herbal substance

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

This assessment report refers only to *Rosa gallica* L., *Rosa centifolia* L., *Rosa damascena* Mill., flos

## 1.2. Information about products on the market in the Member States

### Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination herbal tea
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No marketed products

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

### 1.3. Search and assessment methodology

Search terms: *Rosa gallica* L., *Rosa centifolia* L., *Rosa damascena* Mill., Rosa flos, Rose petals, Rose.

Databases: Pubmed, Medline, HealLink, Scopus.

Libraries: University of Athens, Lab. of Pharmacognosy and Chemistry of Natural Products of the University of Athens.

## 2. Historical data on medicinal use

Roses are best known as ornamental plants grown for their flowers in the garden and sometimes indoors. They have been also used for commercial perfumery and commercial cut flower crops. Some are used as landscape plants, for hedging and for other utilitarian purposes such as game cover and slope stabilisation while they also have medicinal uses (Duke 2002; Madaus 1979). In addition to their perfuming effect, flowers, petals and hips (seed-pot) of *Rosa damascena* are used for medical purposes. Ancient medical books reported several therapeutic uses of this plant such as: treatment of abdominal and chest pain, strengthening the heart, treatment of menstrual bleeding, treatment of digestive problems and anti-inflammatory treatment. North American Indian tribes use a decoction of the root of *Rosa damascena* plant as a remedy to ease cough in children. This plant is also used as a gentle laxative. The essential oil from *Rosa damascena* is reported to have analgesic, hypnotic, antispasmodic and anti-inflammatory effects (Boskabady *et al.* 2006; Duke 2002).

### Names and their origin

The name comes from French 'rose', itself from Latin 'rosa', which was perhaps borrowed from Oscan and from Ancient Greek *ῥόδον* (*rhódon*), related to Old Persian world- Avestan *varada*, Sogdian *ward*, Parthian *war*, Armenian *vard*.

German: Rote Essig- oder weiße Zentifolienrosenblüten;

English: Cabbage rose petals, red-rose petals, rose petals;

French: Fleur de rose pâle et rouge, pétales de rose;

Italian: Fiore di rosa (bianca o rossa);

Spanish: Capullo de rosa, Flor de rosa (blanca o roja), petalos de rosa (Blaschek *et al.* 2006).

Fossil records indicate that *Rosa* species have existed on the planet for at least 40 million years. The earliest historical records on Mesopotamian cuneiform tablets indicate that rose became known to humans about 5,000 years ago.

Assyrian tablets tell of rose and rose water. Cuneiform texts also indicate that the roses were not directly distilled but boiled with water to produce fragrant water. The very small quantities prescribed, as little as one carat (0.2 g), illustrate how precious it was (Baumann 1996).

The apothecary rose, *Rosa gallica officinalis*, first recorded in the 13<sup>th</sup> century, was the foundation of a large industry in the Provence region, France. Turned into jellies, powders and oils; this rose was believed to cure a multitude of illnesses.

Dioscorides (40-90 CE) wrote about rose's cooling and astringent qualities, and that the liquor of roses cooked in wine was useful for treating headaches and ailments of the eyes, ears, gums, anus, and womb. Powdered dried rose flowers were sprinkled on food for pain of the gums (Gennadios 1914).

The Roman naturalist Pliny the Elder (23-79 CE) described rose as astringent and the petals, flowers and heads as useful in medicine. Rose was prescribed for health conditions in many parts of the body, including the head, ears, mouth, gums, tonsils, stomach, rectum and uterus. The flowers taken in oxycrate (a mixture of water and vinegar) were said to arrest flushes in females and blood-spitting, and its fragrance could be inhaled to clear the brain (Gennadios 1914).

The rose oil of the Greek physician Dioscorides was a fatty oil in which roses had been steeped (Gennadios 1914).

In traditional Ayurvedic medicine in India, rosebuds are regarded as astringent and as having cardiac and cephalic tonic properties. The petals are used to relieve uterine haemorrhage and are applied locally for oral ulcer (Can Baser *et al.* 2012).

## **2.1. Information on period of medicinal use in the Community**

No products are currently found on the market in Austria, UK, Germany, Norway, Cyprus, Sweden, Italy, Estonia, Finland, Lithuania, Bulgaria, Czech Republic.

### **Belgium**

Combination products:

Solution for oropharyngeal use since 1962. No data – product no longer marketed since 1976.

Friction solution since 1972. No data – product no longer marketed since 1987.

Friction solution since 1972: methyl nicotinate 2.5 mg/g, camphora synthetica 5 mg/g, nicotinas phenylis 3 mg/g, lemon oil 10 mg/g, rosae flos extr.fluidum 7.5 mg/g, carvacrol 50 mg/g.

Oropharyngeal solution since 1962: boras natrii 90 mg/g, tannic acid 0.6 mg/g, benzoe tinctura 0.8 mg/g, rosae flos extr. fluidum 20 mg/g.

These combinations were registered in Belgium in the past, no distinction was made between active substance and excipients.

Cream: pinus sylvestris aetheroleum 5 mg/g, menthol 5 mg/g, eucalyptol 20 mg/g, camphora synthetica 5 mg/g, thymol 0.5 mg/g, turpentine oil 5 mg/g, lavandulae aetheroleum 1 mg/g, guaiacol 20 mg/g, rosae flos, extr.fluidum 1 mg/g.

### **Spain**

Combination products:

Herbal tea: 1.2 g in boiling water as an infusion.

Composition: Matricariae flos 70%, Sambuci flos 15%, Rosae flos 15%.

Posology: 1.2 to 2.4 g of herbal drug in 250 ml of boiling water as an infusion. Clean the eyes with sterile gauze when the liquid is warm.

Indication: Conjunctivitis.

In 1990, the above-mentioned combination product was registered under the former registration scheme. It was revoked in April 2011.

## France

Three combinations products containing rose flower (composition not specified) are on the market as herbal teas.

Three acceptable therapeutic indications are mentioned in Cahiers de l'Agence n° 3 for rose flower buds and petals:

- Traditionally used in the symptomatic treatment of mild diarrhoea.
- Traditionally used topically as a soothing and antipruriginous application for dermatological ailments and as a protective treatment for cracks, grazes, chapped skin and insect bites.
- Traditionally used locally as a mouth wash for oral hygiene.

### **Other information for traditional therapeutic uses**

#### **Greece** (Fragaki 1969; Gimnasios Lavriotis 1979)

Greek literature mentioned the use of **rose petals** infusion against skin inflammation and for cleaning eyes purposes, in doses of 1-2 g per cup (150 ml) of boiling water.

Uses: Antiseptic, anti-inflammatory and healing (Fragaki 1969).

Dosage: 1-3 times per day.

#### **Commission E** (Blumenthal *et al.* 2000)

Rose flower *Rosae flos/Rosenblüten* 1990, *Rosae flos*, rose flower

**Rose flower** consists of the dried petal of *Rosa gallica* L., *Rosa centifolia* (Fam. Rosaceae) and variations, collected prior to fully unfolding. The **herb** contains tannins.

Uses: Mild inflammations of the oral and pharyngeal mucosa.

Dosage: 1 - 2 g of drug per cup (200 ml) of water for tea.

Action: Astringent

#### **Duke (2002) and PDR for herbal drugs** (Gruenwald *et al.* 2007):

Mode of administration: **Rose flowers** are available as whole crude and powdered drug forms for internal and external uses.

*Preparation:* Tea: 1 to 2 g drug added to cup (200 ml) water.

*Daily Dose:* Tea infusion: up to 3 cups per day. It is also used for rinses and washes.

*Daily Powder:* 5 to 10 g with honey or any liquid.

The **Rose leaves** (referred to petals in the above references) can be applied directly to the eyes.

#### **Hager's** (Blaschek *et al.* 2006):

**Rose flowers** as whole crude and powdered drug forms for internal and external uses.

**Diluted Rose vinegar:** 60 g flowers in 750 ml red wine vinegar, shaken for one week. For body washes.

**Powdered flowers** 5 to 10 g of are administered in fluid (water) or honey, while fresh **rose leaves** may be put directly on the eyes

**Folk medicine and other usage** (referred to all references included within "other information for traditional uses")

External use for minor inflammation of the mucosa of mouth and throat, or for aphthae, spongy wounds and inflammation of eyelids; internally for bleeding, diarrhoea, lung tuberculosis, catarrh of the lung and asthma. The efficacy in these indications is not proven.

Dosage and method of administration: 1 to 2 g **herbal substance** per one cup (200 ml) infusion, for washings, up to three cups also taken for internal use.

## ***2.2. Information on traditional/current indications and specified substances/preparations***

According to the overview of the European market, there are only combination herbal preparations containing rose flower (France, Belgium, Spain) that have been used since at least the last 40 years (according to existing references). The single herbal substance and the comminuted dried petals as infusion are found in literature references with the period of use longer than 30 years (Madaus 1979; Gruenwald *et al.* 2007; Fragaki 1969; Blumenthal *et al.* 2000; Duke 2002).

Therefore for Rose flower a period of at least 30 years in medicinal use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is considered fulfilled. The evidence on traditional medicinal use is confirmed by an existing number of publications providing consistent information.

Herbal substance: whole dried petals

Herbal preparation: comminuted herbal substance

Herbal substance and comminuted herbal substance for infusion preparation for oromucosal or cutaneous use

### **The indications adopted by HMPC**

#### **Indication 1)**

Traditional herbal medicinal product used for mild inflammations of the oral and pharyngeal mucosa.

#### **Indication 2)**

Traditional herbal medicinal product used for relief of minor skin inflammation.

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

### **Posology**

*Adolescents, adults and elderly*

#### **Indications 1) and 2)**

Single dose

Herbal substance or comminuted herbal substance for infusion preparation for oromucosal or

cutaneous use: 1– 2 g of the herbal substance or comminuted herbal substance in 200 ml of boiling water, up to 3 times daily.

Daily dose: 3-6 g

#### Indication 1)

As a mouth rinse, up to 3 times daily.

#### Indication 2)

Infusion preparation for cutaneous use. Apply in form of a wet impregnated dressing.

The use in children under 12 years of age is not recommended.

#### Duration of use

#### Indications 1) and 2)

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

#### Method of administration

Cutaneous use

Oromucosal use

### 3. Non-Clinical Data

#### **3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

##### *In vitro experiments*

##### **Primary pharmacodynamics**

##### *Antimicrobial ability*

Shokouhinejad *et al.* 2010 demonstrated the antimicrobial activity of a plant-derived extract (2% *Rosa damascena* extract, not further specified) together with 5.25% sodium hypochlorite (NaOCl) and 2% chlorhexidine (CHX) on selected endodontic pathogens. The minimum inhibitory concentrations (MICs) of 2% rose extract and 2% CHX for test microorganisms, except *F. nucleatum*, were lower than that of 5.25% NaOCl. All solutions were able to kill all test microorganisms after one minute.

In phytochemical screening of Iranian plants used in traditional therapy for their antimicrobial activities, the highest activity (100% inhibition) was exhibited by a butanol extract of *Rosa damascena* receptacles against *Salmonella typhimurium* and *Bacillus cereus* (MIC of 62.5 and 250 µg/ml) respectively. An aqueous extract of *Rosa damascena* receptacles was active against *Candida albicans* (MIC of 125 µg/ml), while methicillin-resistant *Staphylococcus aureus* was inhibited by butanol, aqueous extracts of *Rosa damascena* receptacles (Talib *et al.* 2010).

##### *Antioxidant activity*

The antioxidant activity of methanolic extracts from fresh flowers of three rose species (*Rosa damascena*, *Rosa bourboniana* and *Rosa brunonii*) was evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) free-radical method. The ability to scavenge DPPH radical was measured by the discoloration of the solution. The methanolic extract from *Rosa brunonii* exhibited maximum free-radical-scavenging

activity ( $64.5 \pm 0.38\%$ ) followed by *Rosa bourboniana* ( $51.8 \pm 0.46\%$ ) and *Rosa damascena* ( $43.6 \pm 0.25\%$ ) at 100 µg/ml (Kumar *et al.* 2009).

For antioxidant activity, the radical scavenging activity, reducing power and phenolic contents of ethanol plant extracts of *Rosa damascena* Mill. were determined. Gallic acid was used as standard reference with well-documented antioxidant activity. The highest antioxidant activity in terms of DPPH radical scavenging was found in *Rosa damascena* with an  $IC_{50}$  equal to  $287.9 \pm 5.675$  µg/ml that was higher than gallic acid ( $IC_{50} = 25.32 \pm 5.593$  µg/ml) (Himesh *et al.* 2012).

#### Assessors comment

Only a few studies exist which can be brought in connection with primary pharmacodynamic effects of *Rosae flos*. One of them was conducted with aqueous extract (Talib *et al.* 2010), while the *in vitro* antioxidant assays were conducted with methanolic and ethanol extracts. All results could be seen as to add some plausibility to the traditional use of the infusion preparation of *Rosae flos*.

### Secondary pharmacodynamics

#### Antisolar agent

*Rosa damascena* flowers were evaluated as an antisolar agent based on their high content on flavonoids. Three different extracts were prepared (water: ethanol 50:50; ethyl acetate: ethanol 80:20 and ether). The hydroalcoholic and ethyl acetate: ethanol extracts were prepared by maceration and the ether extract by soxhletion. The UV absorption spectra (in the range of 200-400 nm) of all extracts of this study were obtained. The hydroalcoholic extract gave the highest sun protector factor (SPF) among the three evaluated different extracts (water: ethanol 50:50; ethyl acetate: ethanol 80:20 and ether), when they were incorporated to the cream base. On the other hand, by performing a few physicochemical tests on the prepared creams, cream containing 5% ether extract showed the most desirable appearance and stability among the creams investigated. The UV absorption ability of these extracts is suggested to be because of the presence of flavonoid compounds within the extracts. However, it should be noted that in order to obtain an effective suncare product with high SPF values, these extracts could be used along with other synthetic antisolar agents (Tabrizi *et al.* 2003).

#### Anti-HIV activities

Water and methanol extracts of *Rosa damascena* exhibited moderate anti-HIV activity. The anti-viral activities of 9 compounds isolated from the methanol extract were compared. The tetrahydroxyflavanone (kaempferol) was effective in reducing the maturation of infectious progeny virus apparently due to selective inhibition of the viral protease. On the other hand, the pentahydroxyflavone (quercetin) and two 3-substituted derivatives of kaempferol appeared to inhibit HIV-infection by preventing binding of gp120 to CD4. 2-Phenylethanol-O-(6-O-galloyl)-β-D-glucopyranoside interacted irreversibly with gp120 and neutralised virus infectivity. The differences in the modes of action of kaempferol and 2-Phenylethanol-O-(6-O-galloyl)-β-D-glucopyranoside can account for the apparent synergy of their anti-viral activities (Gao *et al.* 2013; Can Baser *et al.* 2012). Very recently aurones, isoaurone and damaurones A and B, isolated from the flowers of *Rosa damascena*, were tested for their anti-HIV-1 activities. The results showed that the compound damaurone A had significant potential anti-HIV-1 activity with therapeutic index (TI) values above 80 (Gao *et al.* 2013).

#### Cytotoxic activities

Two aurones (damaurones A and B) isolated from the flowers of *Rosa damascena*, were tested for their cytotoxicities. The results showed that damaurone A had significant high cytotoxicities against NB4 and MCF7 cell lines with  $IC_{50} = 3.4$  and  $2.6$  µM, respectively (Gao *et al.* 2013).

### *Neurite outgrowth activity*

Dementia is a clinical syndrome characterised by multiple cognitive deficits and causes progressive neurodegeneration leading eventually to death. The incidence of dementia is increasing worldwide with the increase in ageing population. It has been hypothesised that drugs activating neurite outgrowth might induce neuronal reconstruction and help in the recovery of brain function. Working on this hypothesis, the authors observed that the chloroform extract of the *Rosa damascena* significantly induced the neurite outgrowth activity and inhibited the A $\beta$ (25-35)-induced atrophy and cell death. Further workup led to the isolation of a very long polyunsaturated fatty acid (molecular formula C<sub>37</sub>H<sub>64</sub>O<sub>2</sub>) as an active constituent. The structure of this compound was established by extensive analysis of fragmentations observed in EI-MS mode. The isolated compound protected A $\beta$ (25-35)-induced atrophy and displayed strong neurite outgrowth activity. The lengths of dendrite in the cells treated with this compound were comparable to those of nerve growth factor-treated cells (Awale *et al.* 2009).

### *Cardiovascular system activity*

*Rosa damascena* has been manufactured as various food products, including tea, in Korea. The flavonoid glycoside roxyloside (kaempferol-3-O- $\beta$ -D-glucopyranosyl(1 $\rightarrow$ 4)- $\beta$ -D-xylopyranoside) as well as isoquercitrin, afzelin and quercetin gentiobioside exhibited high levels of inhibitory activity against 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase with IC<sub>50</sub> values ranging from 47.1 to 80.6  $\mu$ M. Cyanidin-3-O- $\beta$ -glucoside significantly suppressed angiotensin I-converting enzyme (ACE) activity, with an IC<sub>50</sub> value of 138.8  $\mu$ M, while the other four compounds were ineffective. The authors concluded that these results indicate that *Rosa damascena* and its flavonoids may be effective to improve the cardiovascular system (Kwon *et al.* 2010).

### *Anti-aging activity in Drosophila*

The effects of a *Rosa damascena* flower extract (not further specified) on the mortality rate of *Drosophila melanogaster* was evaluated in this study. The authors state that *Rosa damascena* is a potent antioxidant that has many therapeutic uses in addition to its perfuming effects. Supplementing *Drosophila* with this rose extract resulted in a statistically significant decrease in mortality rate in male and female flies. Moreover, the observed anti-aging effects were not associated with common confounds of anti-aging properties, such as a decrease in fecundity or metabolic rate (Jafari *et al.* 2008).

### *Effect on rat ileum*

In a recent research, the effect of an extract of *Rosa damascena* Mill petals (growing in Kashan, Iran) on ileum motility was investigated. The hydroalcoholic extract was prepared by percolation. A section of rat ileum was suspended in an organ bath containing Tyrode's solution. The tissue was stimulated with electrical field stimulation (EFS), KCl and acetylcholine (ACh). The tissue was kept under 1 g tension at 37°C and continuously gassed with O<sub>2</sub>. The effect of the *Rosa damascena* extract was studied on ileum contractions induced by EFS, KCl and ACh and compared with that of atropine. *Rosa damascena* extract (10-100  $\mu$ g/ml) induced a contraction in rat isolated ileum while at 1 mg bath concentration it had relaxant effect on rat ileum. Hydroalcoholic extract of *Rosa damascena* (1-8 mg/ml) concentration dependently inhibited ileum contraction induced by KCl (IC<sub>50</sub>=3.3  $\pm$  0.9 mg/ml), ACh (IC<sub>50</sub>=1.4  $\pm$  0.1 mg/ml) and EFS (IC<sub>50</sub>=1.5  $\pm$  0.3 mg/ml). The vehicle had no significant effect on ileum contractions. From this experiment it was concluded that *Rosa damascena* extract at microgram concentrations had a stimulatory effect on ileum smooth muscle. However, at milligram concentrations, it shows an inhibitory effect. The authors assume that this is most likely due to presence of different components in the extract. The authors conclude that the stimulatory effect of the extract confirms its

benefits for the treatment of constipation and therefore recommend separation and identification of active components (Sadraei *et al.* 2013).

#### Assessors comment

*The interpretation of the results from in vitro studies (anti-HIV/ cytotoxic activities, neurite outgrowth activity, as well as cardiovascular system and rat ileum effects) give presently no sufficient evidence to acknowledge such activities of the preparations of Rose flower.*

#### **In vivo experiments**

##### *Relaxant – hypnotic effects in mice*

*Rosa damascena* has been found to act on central nervous system including brain. It inhibits the reactivity of the hypothalamous and pituitary systems in rat. In traditional medicine a hypnotic effect of Rose is also suggested. The hypnotic effect of ethanolic, aqueous and chloroformic extracts of *Rosa damascena* was investigated in mice. The hypnotic method was based on potentiation of pentobarbital induced sleeping time by extracts. Three doses of extracts (100, 500 and 1,000 mg/kg) were injected i.p. in comparison with diazepam (3 mg/kg) as positive control and saline as negative control. After 30 minutes of injection of the extract, pentobarbital (30 mg/kg) was injected and the increase in sleeping time by extracts was recorded. The results showed that the ethanolic and aqueous extracts in 500 and 1,000 mg/kg doses significantly increased pentobarbital induced sleeping time which was comparable to diazepam. The chloroformic extract had no hypnotic effect (Rakhshandah & Hosseini 2006).

##### *Antidiabetic activity in rats*

The effect of a methanol extract of *Rosa damascena* Mill. flowers was studied, in comparison to the  $\alpha$ -glucosidase inhibitor acarbose, in normal and diabetic rats. The inhibition mode of this extract was examined by measuring enzyme activity in different concentrations of substrate for Lineweaver-Burk plot analysis. The results showed that *Rosa damascena* extract has an intensive inhibitory effect on  $\alpha$ -glucosidase. Its inhibition was found to be non-competitive. Oral administration of this plant extract (100 - 1000 mg/kg body weight) significantly decreased blood glucose after maltose loading in normal and diabetic rats in a dose-dependent manner. These results suggest that *Rosa damascena* might exert an anti-diabetic effect by suppressing carbohydrate absorption from the intestine and can reduce the postprandial glucose level (Gholamhoseinian *et al.* 2009).

##### *Relaxant effects of Rosa damascena on guinea pig tracheal chains*

Several therapeutic effects including hypnotic, antispasmodic, treatment of abdominal and chest pain have been described for the flowers of *Rosa damascena*. Therefore in the study by Boskabady *et al.* 2006, the relaxant effects of an ethanolic extract and essential oils of *Rosa damascena* on tracheal chains of guinea pigs were examined. The relaxant effects of four cumulative concentrations of ethanolic extract (0.25, 0.5, 0.75 and 1 g%) and essential oils (0.25, 0.5, 0.75 and 1 vol.%) in comparison with saline as negative control and four cumulative concentrations of theophylline (0.25, 0.5, 0.75 and 1 mM) were examined by their relaxant effects on precontracted tracheal chains of guinea pig by 60 mM KCl (group 1, n=5) and 10  $\mu$ M methacholine in two different conditions including: non-incubated tissues (group 2, n=8) and incubated tissues with 1  $\mu$ M propranolol and 1  $\mu$ M chlorpheniramine (group 3, n=5). In group 1 experiments, two final concentrations of essential oil and theophylline and only final concentration of ethanolic extract showed relaxant effects compared to that of saline ( $p < 0.01-0.001$ ). In group 2, three higher concentrations of ethanolic extract and theophylline and all concentrations of essential oil showed concentration dependent relaxant effects compared to that of saline ( $p < 0.05-0.001$ ). In addition, the effect of 0.25 and 0.5% w/w of essential oils in group 2

was significantly higher than those of theophylline and ethanolic extract ( $p < 0.01$  for all cases). However, in group 3 experiments the extract and essential oil of *Rosa damascena* did not show any significant relaxant effect. There were significant correlations between the relaxant effects and concentrations for ethanolic extract and essential oil and theophylline in groups 1 and 2. It was concluded that these results showed a potent relaxant effect of *Rosa damascena* on tracheal chains of guinea pigs that was comparable to that of theophylline at concentrations used (Boskabady *et al.* 2006).

#### *Hepatoprotective activity*

In this study, the hepatoprotective activity of the aqueous extract of *Rosa damascena* flowers was investigated at different oral dose levels (250, 500 and 1,000 mg/kg body weight) on acetaminophen (2 g/kg oral N-acetyl-p-aminophenol [APAP])-induced toxicity in rats. APAP administration altered various biochemical parameters, including serum transaminases, serum alkaline phosphatase, lactate dehydrogenase, albumin, bilirubin, urea and creatinine, hepatic lipid peroxidation, and reduced glutathione levels. Adenosine triphosphatase and glucose-6-phosphatase activity in the liver was decreased significantly in animals treated with APAP. These values are retrieved significantly by treatment with *Rosa damascena* extract at all 3 doses in a dose-dependent manner. Apart from these, histopathological changes also reveal the protective nature of the *Rosa damascena* extract against acetaminophen-induced necrotic damage of hepatic tissues. In their conclusion, the authors stated these data suggest that the aqueous extract of *Rosa damascena* may prevent hepatic damage from APAP-induced toxicity in rats and is likely to be mediated through its antioxidant activities (Saxena *et al.* 2012).

#### *Assessors comment*

*Assessing the results of the in vivo studies, there is presently no sufficient evidence to acknowledge a vasorelaxant, antidiabetic or hepatoprotective effect of preparations of aqueous and methanolic extracts of Rosa spp.*

### **3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

No data on Rose flower and preparations thereof have been found or reported.

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

#### **Single-dose and repeat-dose toxicity studies**

No data reported.

#### **Genotoxicity studies**

No data reported.

#### **Carcinogenicity studies**

No carcinogenicity studies carried out on Rose flower in the scientific literature.

## Reproductive and developmental toxicity studies

No reproductive and developmental toxicity studies carried out on Rose flower in the scientific literature.

The safety of Rose flower during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (as infusion preparation or finished products) should not be used during pregnancy and lactation.

### 3.4. Overall conclusions on non-clinical data

Only a few studies exist which can be brought in connection with primary pharmacodynamic effects of *Rosae flos*. One of them was conducted with an aqueous extract (Talib *et al.* 2010), while the *in vitro* antioxidant assays were conducted with methanolic extracts. All results could be seen as to add some plausibility to the traditional use of the infusion preparation of *Rosae flos*. The published data referring to the indications and preparations are limited (Blumenthal *et al.* 2000, PDR 2007, Blaschek *et al.* 2006; Fragaki, 1969; Gimnasios Lavreotis 1979), but existing data on the above-mentioned pharmacological activities support the proposed traditional uses:

#### Indication 1)

Traditional herbal medicinal product used for mild inflammations of the oral and pharyngeal mucosa.

#### Indication 2)

Traditional herbal medicinal product used for relief of minor skin inflammation.

The interpretation of the results from *in vitro* studies (anti-HIV / cytotoxic activities, neurite outgrowth activity, as well as cardiovascular system or rat ileum effects) is presently no sufficient evidence to acknowledge such activities of the preparations of Rose flower; assessing the results of the *in vivo* studies is presently no sufficient evidence to acknowledge the vasorelaxant, antidiabetic or hepatoprotective effect of the aqueous and methanolic extracts of *Rosa* spp.

No published data about pharmacokinetics are available.

No data from investigations concerning single- and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from *Rosae flos* in animals, according to current state-of-the-art standards, are available.

The requirements to establish a Community list entry are not fulfilled.

## 4. Clinical Data

### 4.1. Clinical Pharmacology

#### 4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

#### 4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

## 4.2. Clinical Efficacy

### 4.2.1. Dose response studies

No data available.

### 4.2.2. Clinical studies (case studies and clinical trials)

#### *Recurrent aphthous stomatitis*

Evaluation of a *Rosa damascena* aqueous extract mouthwash in the treatment of recurrent aphthous stomatitis (randomised, double-blinded, placebo-controlled clinical trial)

As the exact aetiology of recurrent aphthous stomatitis remains unknown, its treatment has primarily been palliative to relieve the pain, associated inflammation, and duration of the lesions by using antibacterial mouth rinses, analgesics and immunomodulators. Nevertheless, no treatment has been universally effective in management of recurrent aphthous stomatitis, which necessitates the search for novel therapeutic agents. The aim of this study was to assess the clinical efficacy of the aqueous extract of *Rosa damascena*, for which anti-inflammatory and antinociceptive properties are reported, in the treatment of recurrent aphthous stomatitis. Fifty patients were enrolled in this 2-week study; the clinical efficacy of the mouthwash on pain, size, and number of ulcers in the test group was compared with that of the placebo group on days 4, 7, 11, and 14. Results: There were no statistically significant differences between baseline parameters. However, statistical analysis indicated a significant difference on days 4 and 7 between the placebo and test groups for all parameters. The authors concluded that this study showed that the mouthwash containing *Rosa damascena* extract was more effective than the placebo in the treatment of recurrent aphthous stomatitis (Hoseinpour *et al.* 2011).

#### *Ophthalmic disorders*

Evaluation of eye drops, a herbal combination formulation containing a rose extract, in the management of various ophthalmic disorders.

An open prospective multicentre clinical trial was conducted in patients suffering from various ophthalmic disorders: conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula) and postoperative cataract patients with a herbal eye drop preparation containing basic principles of different herbs which have been conventionally used in the Ayurvedic system of medicine since time immemorial. These include *Carum copticum*, *Terminalia belirica*, *Emblica officinalis*, *Curcuma longa*, *Ocimum sanctum*, *Cinnamomum camphora*, *Rosa damascena* and honey. These herbs reportedly possess anti-infective and anti-inflammatory properties. The present study was undertaken to elucidate the role of this herbal product in a variety of eye ailments. An improvement was observed with the use of the herbal eye drop treatment in most cases. There were no side effects observed during the course of the study and the eye drops were well tolerated by the patients. The authors concluded that the herbal eye drops have a useful role in a variety of infective, inflammatory and degenerative ophthalmic disorders (Biswas *et al.* 2001).

#### *Weight management*

Evaluation of a combination product containing extracts of several plants including *Rosa damascena* in weight management

A double-blind, randomised, parallel-group, placebo-controlled study has been carried out in order to evaluate the effect of orally self-administered product. A proprietary fixed combination of *Garcinia cambogia* extract with calcium pantothenate (standardised for the content of hydroxycitric acid and pantothenic acid) and extracts of *Matricaria chamomilla*, *Rosa damascena*, *Lavandula officinalis* and

*Cananga odorata*, on body weight in overweight and obese volunteers. During a 60-day treatment period, the average reduction in body weight for the group receiving this combination (n = 30) was 4.67% compared with 0.63% for the placebo group (n = 28) (p < 0.0001). Weight losses ≥3 kg were recorded for 23 subjects in the treatment group and only one in the placebo group. The authors concluded that the proposed combination product may represent a potential therapy for obesity (Toromanyan *et al.* 2007).

#### **4.2.3. Clinical studies in special populations (e.g. elderly and children)**

None reported.

### **4.3. Overall conclusions on clinical pharmacology and efficacy**

The traditional use is well documented in literature while the efficacy of the herbal substance and preparation thereof (as an infusion preparation) is plausible on the basis of long-standing use and experience for the administration in adults and adolescents over 12 years of age. Controlled clinical studies required to support a well-established use have not been performed with *Rosae flos* preparations.

Hoseinpour *et al.* 2011, in a randomised, double-blind, placebo-controlled investigation, showed that a mouthwash containing an aqueous *Rosa damascena* extract was more effective than the placebo in the treatment of recurrent aphthous stomatitis, in fifty patients who were enrolled in this 2-week study.

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

There is a lack of clinical and non-clinical safety and toxicity data for Rose flower and further investigation of these aspects is required.

### **5.2. Patient exposure**

A case report was published concerning 13 workers with respiratory symptoms apparently related to occupational exposure to powdered rose hips of *Rosa regulosa*. It was concluded that rose hips are occupational allergens capable of producing asthma (Kwaselov *et al.* 1990).

### **5.3. Adverse events and serious adverse events and deaths**

No data available.

### **5.4. Laboratory findings**

No data available.

### **5.5. Safety in special populations and situations**

#### **Special patient population**

No data on the use in children are available; therefore Rose flower (whole or comminuted dried petals) are intended only for adolescents, adults and elderly.

## **Fertility, pregnancy and lactation**

No fertility data available.

In the absence of sufficient data and in accordance with general medical practice, the use of herbal medicinal products containing Rose flower (whole or comminuted dried petals) is not recommended during pregnancy and lactation.

## **Overdose**

No cases of overdose have been retrieved in the scientific literature search.

## **Drug abuse**

No information in the scientific literature search.

## **Effects on ability to drive or operate machinery or impairment of mental ability**

No data in the scientific literature search.

## **5.6. Overall conclusions on clinical safety**

There are no non-clinical and clinical safety data on Rose flower (whole or comminuted dried petals).

## **6. Overall conclusions**

The positive effects of Rose flower against mild inflammations of the oral and pharyngeal mucosa and in minor skin inflammations have been recognised empirically. The traditional use is made plausible by the long-standing use and experience as well as few *in vitro* and *in vivo* pharmacological data. It is also supported by the findings of a small randomised, double-blinded, placebo-controlled clinical study that showed that a mouthwash containing an aqueous *Rosa damascena* extract was more effective than the placebo in the treatment of recurrent aphthous stomatitis (Hoseinpour et al. 2011).

No clinical studies conducted with preparations containing *Rosa centifolia* and *Rosa gallica* flowers were found.

In conclusion, traditional herbal medicinal products containing Rose flower (dried petals or comminuted dried petals) can be registered in the following indications:

### **Indication 1)**

Traditional herbal medicinal product used for mild inflammations of the oral and pharyngeal mucosa.

### **Indication 2)**

Traditional herbal medicinal product used for relief of minor skin inflammation.

The posology, duration of use and method of administration are given in the monograph and in section 2.2 of this assessment report.

In the absence of sufficient data, use is intended only in adolescents, adults and elderly.

In the absence of sufficient data and in accordance with general medical practice, use is not recommended during pregnancy and lactation.

The use in the specified conditions of use is considered safe. No adverse effects during the use of herbal medicinal products containing Rose dried petals (whole or comminuted) have been reported, for the proposed traditional uses.

As there are no available data on genotoxicity, carcinogenicity, reproductive and developmental toxicity on Rose flower, it is not possible to establish a Community list entry.

## **Annex**

### **List of references**