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)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Rosa gallica* L., *Rosa centifolia* L., *Rosa damascena* Mill., flos
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oromucosal and cutaneous use
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Note: This draft assessment report is published to support the release for public consultation of the draft Community herbal monograph on Rosae flos. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by interested parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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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.
(Weiße Rosenblüten: Flores rosae centifoliae, Flores rosae incarnatae, Flores rosae pallidae, Flos Rosae pallidae, Rosae centifoliae Petala.
Rote Rosenblüten: Flores rosae gallicae, Flores rosae rubrae, Flos Roseae rubrae, Petala rosae rubrae, Rosae Gallicae Petala (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 has 2 monographs on
- *Rosa gallic*a (Rose rouge, 1989i) and
- *Rosa centifolia* (Rose pâle, 1989ii), also in DAC (2012).

***Rosa damascena* Mill.**

Rosa damascena Mill. is an erect shrub 1–2 m in height from the Rosaceae family. 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).
Synonyme: *Rosa bifera* PERS., *Rosa calendarum* BORKH., *Rosa centifolia bifera,* POIRET, *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 pedicles. 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 is 1 to 1.5 cm long.
The plant, the descendant of *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 penfoliate, less frequently trifoliate, have long glanular, dark green above, lighter and bluer below, leaflets. They grow together at the leaf steam that terminate in free tips (Boskabady et al. 2006).

***Rosa centifolia* L.**

Synonyms : Rose pâle PF X, Rose rouge PF X, Flos rosae Helv 5, Flores Rosae EB 6, Red-Rose petal Mar 30.

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 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. The high flavonol content of approximately 16 g/kg on a dry weight basis, rutin, quercitrin, myricetin, quercetin, apigenin, and kaempferol (Kumar et al. 2008; Kwon et al. 2010). 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. New aurones, damaurones A and B were very recently isolated from the flowers of *R. damascena* (Gao et al. 2013)
- Catechin, epicatechin, rutin
- Antocyanins (like cyanidin-3-O-β-glucoside)
- Proanthocyanidins kind of tannins
- Phenolic acids (gallic acid etc, m-coumaric acid,)
- Major carotenoids as the b-carotene, lycopene, rubixanthin, zeaxanthin, 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 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 (the major one being 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 & Aydinli 2005).

- Herbal preparation(s)

- 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 monograph 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 (not mandatory field)
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Herbal teas in the market since at least 1980
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

Member State	Regulatory Status				Comments (not mandatory field)
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Combination herbal tea
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on the market

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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 stabilization while they also have medicinal uses (Duke 1985; Madaus 1979). In addition to its perfuming effect, flowers, petals and hips (seed-pot) of *Rosa damascena* are used for medical purposes. In ancient medical books several therapeutic effects of this plant such as treatment of abdominal and chest pain, strengthening the heart treatment of menstrual bleeding, digestive problems and anti-inflammation are reported. North American Indian tribes use a decoction of the root of *Rosa damascena* plant as a cough remedy to ease children's cough. This plant is also used as a gentle laxative. Essential oil from *Rosa damascena* is reported to have analgesic, hypnotic, antispasmodic and anti-inflammatory effects (Boskabady et al. 2006; Duke 1985).

Names and their origin

The name comes from French 'rose', itself from Latin 'rosa', which was perhaps borrowed from Oscan, 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 oder rossa);

Spanish: Capullo de rosa, Flor de rosa (blanca oder roja), petales 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 (3 grains) [0.2 g] — illustrate how precious it was (Baumann 1996).

The first known paintings of a rose are actually frescoes. The earliest example was discovered in Crete around 1,600 B.C.

The apothecary rose, *R. gallica officinalis*, first recorded in the 13th century, was the foundation of a large industry near the city of Provence, 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). Roman naturalist Pliny the Elder (23-79 CE) described rose as astringent, and wrote that the petals, flowers, and heads were useful in medicine; health conditions for which rose was prescribed represented 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 fluxes 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.

2.1 Information on period of medicinal use in the Community

Herbal Use

No products (Austria, UK, Germany, Norway, Cyprus, Sweden, Belgium, Italy, Estonia, Finland, Lithuania, Bulgaria, Czech Republic).

Belgium (combination products containing rosae flos)

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

Friction solution 1972 No data - product no longer marketed since 1987

Cithymene friction (1972): methyl nicotinate 2.50 mg/g / camphora synthetica 5.00 mg/g/ nicotinas phenylis 3.00 mg/g /lemon oil 10.00 mg/g /rosae (flos, extr.fluidum) 7.50 mg/g carvacrolum 5.00 mg/g /

Another (ROSATBOR) oropharyngeal solution (1962): boras natrii 90.00 mg/g / tannic acid 0.60 mg/g benzoe tinctura 0.80 mg/g rosae (flos, extr.fluidum) 20.00 mg/g. These combinations were registered in Belgium in the past, no distinction is made between active substance and excipients

One cream (SOLUBEOL): pinus (aetheroleum)(sylvestris et al.) 5.00 mg/g
menthol 5.00 mg/g eucalyptol 20.00 mg/g camphora synthetica 5.00 mg/g
thymol 0.50 mg/g turpentine oil 5.00 mg/g lavandulae aetheroleum 1.00 mg/g
guaiacol 20.00 mg/g rosae (flos, extr.fluidum) 1.00 mg/g

Spain

Combination products: Pharmaceutical Form: 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

3 combinations products are on the market as herbal teas.

3 acceptable therapeutic indications are mentioned in the "Cahiers de l'Agence n°3" :

- 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

In Greek literature (Fragaki 1969; Gimnasios Lavriotis 1979), it was referred the use of rose petals infusion against skin inflammation and for cleaning eyes purposes respectively, in doses of 1-2 g for one cup of boiling water (150 ml)

Uses: Antiseptic, anti-inflammatory, healing (Fragaki 1969). Dosage: 1-3 times per day.

Commission E (Blumenthal et al. 2000)

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

Rose flower consists of the dried petal of *Rosa gallica* L., *R. 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

Dosage

Mode of administration: Rose flowers are available as whole crude and powdered drug forms for internal and external uses. The leaves can be applied directly to the eyes.

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

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

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

Duke (1985) and PDR for herbal drugs (Gruenwald et al. 2007)

Hager's (Blaschek et al. 2006)

Diluted Rosevinegar (60 g flowers in 750 ml red wine vinegar, shaken for one week) for body washes.

Folk medicine and other usage: External use for minor inflammation of the mucosa of mouth and throat, or for aphthae, spongeous 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.

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

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 (like in France, Belgium, Spain) where it is used widely since at least the last 40 years (in accordance with existing references), while the herbal substance and the comminuted dried petals as infusion are found in literature references and the period of use is longer than 30 years (Madaus 1979; Gruenwald et al. 2007; Fragaki 1969; Blumenthal et al. 2000; Duke 1985).
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 fulfilled. The evidence on traditional medicinal use is confirmed by a large 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 proposed by MLWP-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 over 12 years of age, adults and elderly
Indications 1) and 2)

Single dose
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)

The infusion is applied cutaneously.

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

Oromucosal use

Cutaneous 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) 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 microg/ml) respectively. An aqueous extract of Rosa damascena receptacles was active against *Candida albicans* (MIC of 125 microg/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-picryl hydrazyl (DPPH) free-radical method. The ability to scavenge DPPH radical was measured by the discoloration of the solution. The methanolic extract from *R. brunonii* exhibited maximum free-radical-scavenging activity (64.5 ± 0.38%) followed by *R. bourboniana* (51.8 ± 0.46%) and *R. damascena* (43.6 ± 0.25%) at 100 microg/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. (RD) 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 RD with an IC_{50} equal to 287.9 ± 5.675 µg/ml that was higher than gallic acid (IC_{50} = 25.32 ± 5.593 µg/ml) (Himesh et al. 2012).

Assessor´s 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 antioxidative 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.

Secondary pharmacodynamics

Antisolar agent

Based on the findings, the hydroalcoholic extract seems to give the highest SPF among the three extracts evaluated, when 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)-beta-D-glucopyranoside interacted irreversibly with gp120 and neutralized virus infectivity. The differences in the modes of action of kaempferol and 2-Phenylethanol-O-(6-O-galloyl)-beta-D-glucopyranoside can account for the apparent synergy of their anti-viral activities (Can Baser et al. 2012).

Very recently aurones and isoaurone, 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} values of 3.4 and 2.6 μM, respectively (Gao et al. 2013).

Neurite outgrowth activity

Dementia is a clinical syndrome characterized 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 hypothesized 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 Aβ(25-35)-induced atrophy and cell death. Further workup led the isolation of a very long polyunsaturated fatty acid (molecular formula C(37)H(64)O(2)) 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 Aβ(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).

Activity to cardiovascular system

Rosa damascena has been manufactured as various food products, including tea, in Korea. The flavonoid glycoside, kaempferol-3-O-beta-D-glucopyranosyl(1-->4)-beta-D-xylopyranoside, named roxyloside 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_{50} values ranging from 47.1 to 80.6 microM. Cyanidin-3-O-beta-glucoside significantly suppressed angiotensin I-converting enzyme (ACE) activity, with an IC_{50} value of 138.8 microM, while the other four compounds were ineffective. The authors concluded that these results indicate that *R. damascena* and its flavonoids may be effective to improve the cardiovascular system (Kwon et al. 2010).

Anti-aging activity against Drosophila

The effects of a rose flower extract, *Rosa damascena*, on the mortality rate of *Drosophila melanogaster* was evaluated in this study. *R. 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. 2006; 2008).

Effect on rat ileum

In a recent research, the effect of an extract of flower petals of *R. damascena* Mill. growing in Kashan, Iran, on ileum motility was investigated. Hydroalcoholic extract was prepared by percolation method. 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 O2. Effect of the *R. damascena* extract was studied on ileum contractions induced by EFS, KCl and ACh and compared with that of atropine. R. *damascena* extract (10-100 µg/ml) induced a contraction in rat isolated ileum while at 1 mg bath concentration it had relaxant effect on rat ileum. Hydroalcoholic extract of *R. damascena* (1-8 mg/ml) concentration dependently inhibited ileum contraction induced by KCl (IC_{50}=3.3 ± 0.9 mg/ml), ACh (IC_{50}=1.4 ± 0.1 mg/ml) and EFS (IC_{50}=1.5 ± 0.3 mg/ml). The vehicle had no significant effect on ileum contractions. From this experiment it was concluded that *R. damascena* extract at microgram concentrations had stimulatory effect on ileum smooth muscle. However, at milligram concentrations, it shows an inhibitory effect. This is most likely due to presence of different components in the extract. The stimulatory effect of the extract confirms its benefits for the treatment of constipation. Therefore, separation and identification of active components is recommended (Sadraei et al. 2013).

Assessor´s comment

The interpretation of the results from in vitro studies (anti-HIV / cytotoxic activities, neurite outgrowth activity, as well as to cardiovascular system or to rat ileum) 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 hypnotic effect of Rose is also suggested. In the present study, the hypnotic effect of ethanolic, aqueous and chloroformic extracts of *R. damascena* was investigated in mice. 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 (Rakhshadah & 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 show 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 to 1,000 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 this study by Boskabady et al. (2006), the relaxant effects of 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 microM methacholine in two different conditions including: non-incubated tissues (group 2, n=8) and incubated tissues with 1 microM propranolol and 1 microM 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 g% 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. 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* (RD) 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 RD extract at all 3 doses in a dose-dependent manner. Apart from these, histopathological changes also reveal the protective nature of the RD extract against acetaminophen-induced necrotic damage of hepatic tissues. In their conclusion, the authors stated these data suggest that the aqueous extract of RD may prevent hepatic damage from APAP-induced toxicity in rats and is likely to be mediated through its antioxidant activities (Saxena et al. 2012).

Assessor´s comment

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

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* antioxidative 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. Moreover, the published data referring to the indications and preparations is limited, but existing data on the above-mentioned pharmacological activities ((Blumenthal et al. 2000, PDR 2007, Blaschek et al. 2006; Fragaki, 1969; Gimnasios Lavreotis 1979) 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 to cardiovascular system or to rat ileum) 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 or antidiabetic and hepatoprotective effect of the aqueous and methanolic extracts of *Rosa* sp.

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* extract mouthwash in the treatment of recurrent aphthous stomatitis: a 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 mouthrinses, 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*, which has reported anti-inflammatory and antinociceptive properties, in the treatment of recurrent aphthous stomatitis. This was a randomised, double-blind, placebo-controlled investigation. 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).

Ophtalmic disorders

Evaluation of Ophthacare® 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 namely, conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula) and postoperative cataract patients with a herbal

eye drop preparation (Ophthacare®) 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 meldespumapum. 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. Side effects, if any, were noted during the study. 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 drop was well tolerated by the patients. The authors concluded that the herbal eye drop Ophthacare® has 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 Slim339®, a proprietary fixed combination of *Garcinia cambogia* extract with calcium pantothenate (standardized 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 Slim339® (n = 30) was 4.67% compared with 0.63% for the placebo group (n = 28) ($p < 0.0001$). Weight losses of >or=3 kg were recorded for 23 subjects in the treatment group and only one in the placebo group. The authors concluded that Slim339® 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,* where 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

5.6. 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) can be 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.

5.7. 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 use is made plausible by the long-standing use and experience as well as existing *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