WHO monographs on selected medicinal plants

Volume 3

WHO published Volume 1 of the WHO monographs on selected medicinal plants, containing 28 monographs, in 1999, and Volume 2 including 30 monographs in 2002. This third volume contains an additional collection of 32 monographs describing the quality control and use of selected medicinal plants.

Each monograph contains two parts, the first of which provides pharmacopoeial summaries for quality assurance purposes, including botanical features, identity tests, purity requirements, chemical assays and major chemical constituents. The second part, drawing on an extensive review of scientific research, describes the clinical applications of the plant material, with detailed pharmacological information and sections on contraindications, warnings, precautions, adverse reactions and dosage. Also included are two cumulative indexes to the three volumes.

The WHO monographs on selected medicinal plants aim to provide scientific information on the safety, efficacy, and quality control of widely used medicinal plants; provide models to assist Member States in developing their own monographs or formularies for these and other herbal medicines; and facilitate information exchange among Member States. WHO monographs, however, are not pharmacopoeial monographs, rather they are comprehensive scientific references for drug regulatory authorities, physicians, traditional health practitioners, pharmacists, manufacturers, research scientists and the general public.

ISBN 978 92 4 154702 4
Selected WHO publications of related interest

Information on medicinal plants:

WHO monographs on selected medicinal plants, Volume 2
(ISBN 92 4 154537 2), 2002
WHO monographs on selected medicinal plants, Volume 1
(ISBN 92 4 154517 8), 1999

Quality assurance and control of herbal medicines:

WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants
(ISBN 92 4 154627 1), 2003
Quality control methods for medicinal plant materials
(ISBN 92 4 154510 0), 1998
Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms

Good manufacturing practices: Updated supplementary guidelines for the manufacture of herbal medicines, Annex 3 of WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-fourth report

Regulation, evaluation and safety monitoring of herbal medicines:

Summary report of the global survey on national policy on traditional medicine and complementary/alternative medicine and regulation of herbal medicines
(ISBN 92 4 159323 7), 2005
WHO guidelines on safety monitoring and pharmacovigilance of herbal medicines
(ISBN 92 4 159221 4), 2004
General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine

Consumer information:

WHO guidelines on development of consumer information on proper use of traditional medicine and complementary/alternative medicine
(ISBN 92 4 159170 6), 2004

Further information on WHO technical documents in the field of traditional medicine including those listed above, can be found at the address below:
http://www.who.int/medicines/areas/traditional/
WHO
monographs
on selected
medicinal plants

VOLUME 3
## Contents

Acknowledgements     v
Introduction     1
General technical notices     5

**Monographs (in alphabetical order of plant name)**

<table>
<thead>
<tr>
<th>Monograph</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructus Ammi Majoris</td>
<td>9</td>
</tr>
<tr>
<td>Fructus Ammi Visnagae</td>
<td>23</td>
</tr>
<tr>
<td>Fructus Anethi</td>
<td>33</td>
</tr>
<tr>
<td>Aetheroleum Anisi</td>
<td>42</td>
</tr>
<tr>
<td>Fructus Anisi</td>
<td>53</td>
</tr>
<tr>
<td>Semen Armenicae</td>
<td>64</td>
</tr>
<tr>
<td>Flos Arnicae</td>
<td>77</td>
</tr>
<tr>
<td>Folium Azadirachti</td>
<td>88</td>
</tr>
<tr>
<td>Oleum Azadirachti</td>
<td>102</td>
</tr>
<tr>
<td>Flos Carthami</td>
<td>114</td>
</tr>
<tr>
<td>Stigma Croci</td>
<td>126</td>
</tr>
<tr>
<td>Fructus Foeniculi</td>
<td>136</td>
</tr>
<tr>
<td>Radix Gentianae Luteae</td>
<td>150</td>
</tr>
<tr>
<td>Radix Gentianae Scabrae</td>
<td>160</td>
</tr>
<tr>
<td>Gummi Gugguli</td>
<td>169</td>
</tr>
<tr>
<td>Radix Harpagophyti</td>
<td>182</td>
</tr>
<tr>
<td>Rhizoma Hydrastis</td>
<td>194</td>
</tr>
<tr>
<td>Radix Ipecacuanhae</td>
<td>204</td>
</tr>
<tr>
<td>Aetheroleum Lavandulae</td>
<td>219</td>
</tr>
<tr>
<td>Flos Lavandulae</td>
<td>229</td>
</tr>
<tr>
<td>Strobilus Lupuli</td>
<td>236</td>
</tr>
<tr>
<td>Gummi Myrrha</td>
<td>247</td>
</tr>
<tr>
<td>Herba Passiflorae</td>
<td>257</td>
</tr>
<tr>
<td>Testa Plantiginis</td>
<td>268</td>
</tr>
<tr>
<td>Radix Rehmanniae</td>
<td>283</td>
</tr>
</tbody>
</table>
Contents

Fructus Schisandrae 296
Radix Scutellariae 314
Radix cum Herba Taraxaci 328
Semen Trigonellae Foenugraeci 338
Cortex Uncariae 349
Fructus Zizyphi 359

Annex 1
Participants in the Third WHO Consultation on Selected Medicinal Plants, The Governmental Conference Centre, Ottawa, Canada, 16–19 July, 2001 370

Annex 2
Cumulative index (in alphabetical order of plant name) 373

Annex 3
Cumulative index
(in alphabetical order of plant material of interest) 375
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Sincere appreciation is extended to Health Canada, who hosted the above-mentioned WHO Consultation with its financial support, and to the Regional Government of Lombardy, Italy, which provided funds for the editing and printing of this volume.

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Introduction

Increasing role of the WHO monographs on selected medicinal plants
Since 1999, WHO has published two volumes of the WHO monographs on selected medicinal plants. Volume 1 includes 28 monographs and volume 2 contains an additional 30 monographs. Both of these volumes are now available on the WHO web site http://www.who.int/medicines/organization/trm/orgtrmstrat.htm).

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role. For example, in the recent WHO global survey on national policy and regulation of herbal medicines, of the 34 countries reporting that they do not have their own national monographs and use other monographs, 13 use the WHO monographs as an authoritative reference. Moreover, the format of the WHO monographs continues to be commonly used for developing national monographs. In the same survey, of the 46 countries that have already developed national monographs on herbal medicines, several countries, such as Armenia, Bhutan, Brazil, Malaysia, and Myanmar, reported having used the WHO format as a basis.

In May 2002, WHO launched its Traditional Medicine Strategy covering the period 2002–2005. In 2003, the World Health Assembly adopted resolution WHA56.31 on traditional medicine, which requests WHO to seek, together with WHO collaborating centres, evidence-based information on the quality, safety and cost-effectiveness of traditional therapies. The objective is to provide guidance to Member States on the definition of products to be included in national directives and proposals on traditional-medicine policy implemented in national health systems. The continued development of the WHO monographs on selected medicinal plants is one of the important activities being undertaken to meet the demands from Member States and in the implementation of the WHO Traditional Medicine Strategy.

Preparation of monographs for volume 3
During the preparation of volume 3, more than 170 experts were involved, in addition to members of WHO’s Expert Advisory Panel on Traditional
Introduction

Medicine, a significant expansion in comparison to the numbers involved in the first two volumes. National drug regulatory authorities in 65 countries participated in the process, again a greater number than for the previous volumes. This global network of active players facilitated wider access to the available scientific references and information, in terms of both quality and quantity. This considerable level of support contributed greatly to the efficiency of the preparation process.

The Third WHO Consultation on Selected Medicinal Plants was held in Ottawa, Canada, in July 2001 to review and finalize the draft monographs. Thirty-two experts and drug regulatory authorities from WHO Member States participated (Annex 1). Following extensive discussion, 31 of the 33 draft monographs were adopted for inclusion.

At the subsequent tenth International Conference of Drug Regulatory Authorities held in China, Hong Kong Special Administrative Region in June 2002, the 31 draft monographs adopted for volume 3 of the WHO monographs on selected medicinal plants were presented. In its recommendations, the Conference requested WHO to publish them as soon as possible.

Selection of medicinal plants
The selection of medicinal plants for inclusion in the WHO monographs is based on worldwide use. The medicinal plants selected must meet two major criteria: (1) they must be in common use in at least two WHO Regions; and (2) there must be sufficient scientific data available to satisfy the requirements of the various sections in the monograph format.

The Third WHO Consultation on Selected Medicinal Plants discussed the selection criteria and made recommendations that will be applied starting with the preparation of volume 4 of the WHO monographs.

Changes in format in volume 3
Following intensive discussion at the Ottawa Consultation the title and context of the three categories included in the section Medicinal uses has been changed. The changes are described in the in the General technical notices.

It was also decided at the Ottawa Consultation that the section on Adverse reactions should be moved to follow immediately after the section on Pharmacology, to provide a more logical progression for the subsequent sections on Contraindications, Warnings and Precautions.

A description of selected sections of the monographs is given in the General technical notices, which reflect the above-mentioned format changes. For easy reference, two cumulative indexes are provided as an-
nlexes. Annex 2 lists the monographs in alphabetical order of the plant name, while Annex 3 is according to the plant materials of interest.

Under the section “Geographical distribution”, an attempt has been made to describe the geographical distribution of the plant, i.e. its natural distribution, where it is cultivated, and conditions of cultivation, harvesting and storage. This has been a challenge, owing to the lack of data based on established national good agricultural practices and/or good collection practices for medicinal plants. In 2003, WHO published the WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants, which provide general technical guidance on obtaining medicinal plant materials of good quality for the sustainable production of herbal medicines in the overall context of quality assurance and control of herbal medicines. It is hoped that these guidelines will facilitate the development of GACP monographs on specific medicinal plants at national level, which in turn should bridge the current information gap in this area.

**Purpose and content of monographs**

The purpose of the monographs was clearly explained in the introduction to volume 1, and it is unnecessary to repeat it here. But I would like to emphasize again that the word “monograph” is used as a technical term only. It does not have the same meaning as “monograph” in any type of pharmacopoeia. In addition, I must reaffirm that this publication is not intended to replace any official compendia such as pharmacopoeias, formularies or legislative documents.

It should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO’s official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

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General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO’s Member States; to provide models to assist WHO’s Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO’s Member States.

The format used for volume 3 essentially follows that of volume 2. However, to keep relevant sections together, Adverse reactions appears immediately after the section on Pharmacology. The titles of three categories under the Medicinal uses have been changed to the following:

- Uses supported by clinical data
- Uses described in pharmacopoeias and well established documents
- Uses described in traditional medicine

The Definition provides the Latin binomial name, the most important criterion in quality assurance. Latin binomial synonyms and vernacular names, listed in Synonyms and Selected vernacular names respectively, are names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Code of Botanical Nomenclature. The vernacular names comprise an alphabetical list of selected names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. They refer to the medicinal plant itself not the medicinal plant part, which is identical to the monograph name. The lists are not complete, but reflect the names of the concerned medicinal plant appearing in the official monographs and reference books consulted and those in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, Chicago, IL, USA). While every effort has been made to delete names referring to the
medicinal plant part, the relevant section of each monograph may still include these.

Geographical distribution is not normally found in official compendia, but is included here to provide additional quality assurance information. The detailed botanical description under Description is intended for quality assurance at the stages of production and collection; the description of the crude drug material under Plant material of interest is for the same purpose at the manufacturing and commerce stages.

General identity tests, Purity tests and Chemical assays are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with national requirements by the appropriate authorities of Member States.

Each medicinal plant and the specific plant part used as crude drug material contain active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the Major chemical constituents.

Descriptions included in Medicinal uses should not be taken as implying WHO’s official endorsement or approval for such uses. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange.

The first category, Uses supported by clinical data, includes medical indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. Clinical trials may be controlled, randomized, double-blind studies, open trials, cohort studies or well documented observations on therapeutic applications.

The second category, Uses described in pharmacopoeias and well established documents, includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or governmental monographs. Uses having a pharmacologically plausible basis are also included, as well as information resulting from clinical studies that clearly need to be repeated because of conflicting results.

The third category, Uses described in traditional medicine, refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. Their appropriateness could not be assessed, because sufficient data to support the claims could not be found in the literature. Traditional uses that address severe pathologies, such as cancer, AIDS, hepatitis, etc., as they relate to these modern biomedical terms, should only be included under the third heading if pharmacological data
or robust ethnopharmacological/ethnobotanical reports are available to support the claims.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Abbreviated details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included, to avoid confusion.

The details included in the *References* have been checked against the original sources wherever possible. For references in languages other than English, except for those in Chinese and Japanese, the title is given in the original language, except in cases where an English summary is available.
Fructus Ammi Majoris

Definition
Fructus Ammi Majoris consists of the dried ripe fruits of Ammi majus L. (Apiaceae) (1, 2).

Synonyms
Apium ammi Crantz, Selinum ammoides E.H.L. Krause (3). Apiaceae are also known as Umbelliferae.

Selected vernacular names
Aatrilal, ammi commun, bishop’s weed, bullwort, crow’s foot, cumin royal, devil’s carrot, gazar el-shitan, greater ammi, habab, herb william, hirz al-shayateen, khella shaitani, khella shitany, mayweed, nounkha, qciba, rejl el-ghorab, rijl al-tair, zfenderi el maiz (1, 2, 4–6).

Geographical distribution
Indigenous to Egypt, and widely distributed in Europe, the Mediterranean region and western Asia. Cultivated in India (2).

Description
An annual, 0.9–1.5 m high with striated subglaucous stems. Leaves acutely serrulate, alternate, bipinnate, lobes oblong. Inflorescence a compound umbel with slender primary rays up to 5 cm long, scattered secondary rays 2–5 cm long, minute reticulate points; involucre of bracts 1.5–2.5 cm long; flowers bisexual, polygamous, bracteate; calyx teeth obsolete or small; petals obovate with an inflexed point, exterior petals frequently longer; stamens epigynous; ovary inferior, two-locular, stigma capitate. Fruit laterally compressed, oblong, mericarps of the cremocarp separated by a carpophore. Seed small, pendulous, albuminous (2).
Plant material of interest: dried ripe fruits

General appearance
Cremocarp nearly cylindrical, usually separated into its two mericarps, rarely entire, with a part of the pedicel attached. Mericarp small, slightly concave on the commissural side, slightly tapering towards the apex; 2.0–2.5 mm long, 0.75 mm wide, reddish-brownish to greenish-brown, crowned with a nectary, disc-like stylodop. Externally glabrous, rough, marked with five broad, distinct, yellowish-brown primary ridges, alternating with four equally prominent, dark brown secondary ridges. Internally comprises a pericarp with six vittae, four in the dorsal and two in the commissural side, and a large orthospermous endosperm in which is embedded a small apical embryo. Carpophore forked, each branch entering at the apex of the mericarp and uniting with the raphe (1, 2).

Organoleptic properties
Odour: slightly aromatic, terebinthinate; taste: aromatic, strongly pungent, slightly bitter (1).

Microscopic characteristics
Epidermis of the pericarp consists of polygonal cells, with straight anticlinal walls and short papillae, containing cluster or prismatic crystals of calcium oxalate, and covered with a strongly striated cuticle; stomata, occasionally of the anisocytic type, but with no trichomes. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, four in the dorsal and two in the commissural side, which appear elliptical in transverse section, each surrounded by large, radiating cells; traversed in the primary ridges by vascular bundles, which appear oval, ovoid or rounded in transverse section, not accompanied by vittae, each bundle with a xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres and reticulate, lignified cells. Innermost layer consists of large, polygonal, brown-walled cells, with thick, non-porous inner walls. Endocarp composed of narrow, tangentially elongated cells, many in regular arrangements in variously oriented groups (e.g. parquet arrangement), adhering to the brown seed coat, which is formed of similar but wider and shorter cells. Endosperm consists of polygonal, thick-walled, cellulosic parenchyma, containing fixed oil and several aleurone grains, 4–12 μm in diameter, each with one or two rounded globoid and one or two microrosette crystals of calcium oxalate, 2–5 μm in diameter. Carpophore, each branch traversed by a vascular bundle of fibres and spiral vessels (1, 2, 7).
Powdered plant material
Yellowish-brown and characterized by fragments of epicarp with polygonal, subrectangular or elongated, short, papillose cells, containing cluster or prismatic crystals of calcium oxalate, and covered with thick, distinctly striated cuticle. Also present are fragments of mesocarp with brownish pieces of vittae, reticulate cells, vessels and fibres; fragments of endocarpal cells with a distinct parquet arrangement, usually adhering to brown cells of the testa; numerous fragments of the endosperm containing colourless, polygonal cells, numerous oil globules and several aleurone grains, 4–12 μm in diameter, each enclosing microrosette crystals of calcium oxalate, 2–5 μm in diameter. Trichomes and starch grains absent (1, 2).

General identity tests
Macroscopic and microscopic examinations, microchemical tests (1, 2), and thin-layer chromatography for the presence of xanthotoxin and bergapten (8).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (9).

Total ash
Not more than 7% (1, 2).

Acid-insoluble ash
Not more than 0.04% (2).

Water-soluble extractive
Not less than 17% (2).

Alcohol-soluble extractive
Not less than 16% (2).

Loss on drying
Not more than 12% (1).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (10). For other pesticides, see the European pharmacopoeia (10), and the WHO guidelines on quality control methods for medicinal plants (9) and pesticide residues (11).
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (9).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (9) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.5% xanthotoxin, 0.3% imperatorin and 0.01% bergapten, determined by spectrophotometry (1). A high-performance liquid chromatography method is also available for quantitative analysis (12).

Major chemical constituents
The major constituents are furanocoumarins, the principal compounds being xanthotoxin (methoxsalen, 8-methoxypsoralen (8-MOP) amidinin; up to 1.15%), imperatorin (ammidin; up to 0.75%) and bergapten (heraclin, majudin, 5-methoxypsoralen (5-MOP), up to 1.88%). Other coumarins of significance are marmesin (up to 0.25%), isoimperatorin (0.01%), heraclenin (0.07%) and isopimpinellin (0.01%). Other constituents of interest are acetylated flavonoids (13–17). The structures of xanthotoxin, imperatorin and bergapten are presented below.

Medicinal uses
Uses supported by clinical data
Treatment of skin disorders such as psoriasis and vitiligo (acquired leukoderma) (1, 5, 18–26).

Uses described in pharmacopoeias and well established documents
Treatment of vitiligo (1).