European Food Safety Authority

EFSA Journal 2013;11(7):3302

SCIENTIFIC OPINION

Scientific Opinion on the evaluation of the safety in use of Yohimbe (Pausinystalia yohimbe (K. Schum.) Pierre ex Beille)[1]

EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Additives and Nutrient Sources added to Food provides a scientific opinion evaluating the safety in use of yohimbe bark and its preparations originating from Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille when used in food, e.g. in food supplements. The bark of the plant contains a number of indole alkaloids of biological relevance and preparations of yohimbe bark have been traditionally used as general tonic, performance enhancer and as an aphrodisiac. Food supplements containing yohimbe bark preparations are available nowadays, especially via internet retail. Yohimbine, the major alkaloid of yohimbe bark and raubasine, another alkaloid occurring in lower concentrations in the bark, are used as active ingredients in a number of medicinal products for which adverse effects are described. The Panel reviewed the available scientific data on a possible association between the intake of yohimbe bark and its preparations and potential harmful effects on health. When those data were not available, priority was given to yohimbine, as the only alkaloid for which occurrence had been shown and quantified in food supplements containing yohimbe bark. The Panel concluded that the chemical and toxicological characterisation of yohimbe bark and its preparations for use in food are not adequate to conclude on their safety as ingredients of food, e.g. in food supplements. Thus the Panel could not provide advice on a daily intake of yohimbe bark and its preparations that do not give rise to concerns about harmful effects to health. An estimation of exposure to yohimbine from food supplements was performed showing that theoretical maximum daily intake may exceed the maximum approved daily dose of yohimbine from use as a medicinal product.

KEY WORDS

Yohimbe, Pausinystalia yohimbe, yohimbe bark, yohimbine, raubasine, food supplement, CAS Registry No 146-48-5

---

[1] On request from the European Commission, Question No EFSA-Q-2012-00228, adopted on 03 July 2013.

[2] Panel members: Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Pierre Galtier, David Gott, Ursula Gundert-Remy, Jürgen König, Claude Lambré, Jean-Charles Leblanc, Pasquale Mosesso, Alicja Mortensen, Agneta Oskarsson, Dominique Parent-Massin, Martin Rose, Ivan Stankovic, Paul Tobback, Ine Waalkens-Berendsen, Ruud Woutersen and Matthew Wright. Correspondence: ans@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Botanicals in Food: Ulla Beckman-Sund, Leon Brimer, Birgit Dusemund, Pierre Galtier, Ursula Gundert-Remy, Ivan Stankovic, Jaroslav Toth, Jacqueline Wiesner and Ruud Woutersen for the preparatory work on this scientific opinion and EFSA staff: Davide Arcella and Camilla Smeraldi for the support provided to this scientific opinion.

Suggested citation: EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food), 2013. Scientific Opinion on the evaluation of the safety in use of Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille). EFSA Journal 2013;11(7):3302, 46 pp. doi:10.2903/j.efsa.2013.3302

Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) was asked to deliver a scientific opinion on the evaluation of Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille) in accordance with Article 8 (2) of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods. This request was triggered by the concerns raised by one of the EU Member States on the possible harmful effects associated with the intake of Yohimbe preparations, for example in food supplements.

In particular, EFSA was requested to review the existing scientific data on the possible link between the intake of Yohimbe and harmful effects on health, and to provide advice on a tolerable upper intake level (UL) for Yohimbe for the general population, and as appropriate, for vulnerable subgroups of the population. In the absence of a tolerable upper intake level, the Panel was asked to provide advice on a daily intake of Yohimbe that does not give rise to concerns about harmful effects to health.

In addressing this request, the ANS Panel considered that the term "tolerable upper intake level", so far only used by EFSA to provide guidance on the intake of nutrients, such as vitamins or minerals, may not be appropriate for botanicals and botanical preparations being constituents of food supplements or other food products, especially in cases where the botanicals/botanical preparations or their main components have known medical uses based on scientifically established pharmacological properties and/or where the botanicals/ botanical preparations cannot be regarded as components of the normal diet.

Preparations obtained from the bark of Yohimbe have been traditionally used in West Africa as general tonic, as a performance enhancer for athletes and as an aphrodisiac. The plant *Pausinystalia yohimbe* (K. Schumann) Pierre ex Beille grows in Tropical West Africa (Cameroon, Congo, Gabon, Equatorial Guinea, Nigeria).

Nowadays, despite the use of yohimbe bark and its preparations is specifically prohibited in foods or food supplements in several European countries (e.g. United Kingdom, Ireland, Netherlands, Belgium, Denmark, Czech Republic) as well as in Canada, Australia and New Zealand, these are nonetheless easily available via the internet retail, also in combination with other substances (e.g. caffeine). These products are promoted to improve sexual and athletic performance and for the enhancement of sexual satisfaction and also for weight loss.

A number of indole alkaloids of biological relevance are contained in the bark of the trunk and branches of Yohimbe, yohimbine being the main one. Yohimbine is an antagonist acting at α_2-adrenoreceptors found both in the central nervous system and at peripheral level. It enhances noradrenaline release and increases sympathetic activity. Other alkaloids with proven or potential biological activity have been reported to occur in the bark, such as raubasine (also known as ajmalicine), an α_1-adrenoreceptors antagonist, corynanthine and a number of other stereoisomers of yohimbine.

Quantitative data on the chemical composition of the alkaloids in yohimbe bark and its preparations are limited and extremely variable, depending on a number of factors, such as growing and harvesting conditions of the plant and the analytical method used for quantification. The reported value of total alkaloid content of the bark ranges from about 2 to over 150 mg/g. The most frequently reported concentration for yohimbine is around 10 mg/g whereas for the individual stereoisomers of yohimbine the reported values are in the range of 0.2 to 4.6 mg/g. The concentration of raubasine is reported to be around 0.4 mg/g.

No information was found on the standardisation of the extracts for use in food with regard to the ratio of extracted material to starting material, extraction solvent, and content of biologically active ingredients.

There are no official inter-laboratory validated methods for the determination of yohimbine and accompanying alkaloids in food supplements, although a single-laboratory validated method for the determination of yohimbine in commercial products has been described.

In the absence of data for the individual botanical/botanical preparation, the ANS Panel looked at the information available in the open literature and at information gathered through the relevant food sector organisations and the European Medicines Agency for what concerns the use of yohimbe bark and its individual alkaloids as medicinal products.

No traditional medicinal products containing yohimbe bark and its preparations appear to be authorised or registered in the EU, and an assessment report on the safety and efficacy of this botanical is not available or currently expected from the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency.

Regarding yohimbe bark preparations in food supplements, some information was found on the concentration of yohimbine. In studies aimed at measuring the actual content of yohimbine versus the one declared on the label, it was found that yohimbine content ranged from none up to 18.8 mg/serving. Quantitative data for the other yohimbe alkaloids are not available but would also be required in view of their known or potential biological activity.

Yohimbine, the main alkaloid of yohimbe bark, in its hydrochloride form, is the active ingredient of a number of medicinal products authorised in several EU countries. It is given orally in the treatment of erectile dysfunction in doses of 5–10 mg, 2–3 times daily, the typical treatment period being 8 weeks.

Raubasine, another alkaloid contained in yohimbe bark, is also the active ingredient of some medicinal products. Oral formulations of medicinal products containing raubasine are used as an adjuvant in the treatment of peripheral arterial disorders. The dose is 10–20 mg, 2–3 times daily.

In the absence of data on exposure to yohimbe bark and its preparations, an assessment of the exposure to yohimbine from food supplements was performed using the data obtained from the literature on the measured content of yohimbine in food supplements. The maximum reported content of yohimbine in food supplements was multiplied by the number of maximum suggested servings per day. According to this estimate, exposure to yohimbine from food supplements intake could be up to 75 mg/person/day, which is higher than the approved daily dose of yohimbine from use as a medicinal product (up to 30 mg/person/day).

In general, botanicals such as yohimbe bark and botanical preparations such as yohimbe bark extracts for use in food supplements should be evaluated based on existing data on the chemical specifications and existing toxicological data, including read across where appropriate, for the individual botanical/botanical preparation. Therefore, the Panel gave priority to the toxicological studies investigating yohimbe bark and its preparations. Furthermore, toxicological data on yohimbine were assessed, since this is the main alkaloid in yohimbe bark and the only alkaloid for which occurrence had been shown and quantified in food supplements containing yohimbe bark. In this respect the Panel noted that interactions of yohimbine with other alkaloids present in the bark may occur.

No data are available describing the absorption, distribution, metabolism and excretion of yohimbe alkaloids after oral administration of yohimbe bark preparations such as extracts. When administered to humans, yohimbine is rapidly absorbed and its bioavailability is reported to range widely from 7 % to 87 %. In the liver, yohimbine undergoes oxidation to its pharmacologically active metabolite 11-hydroxy-yohimbine. This metabolic pathway is dependent on the two cytochrome P450 polymorphic variants CYP2D6 and CYP3A4. The great interindividual variability in the clinical effects observed may be attributable to the differences in the hepatic metabolism.

No short-term or (sub)chronic toxicity and carcinogenicity studies on yohimbe bark or its preparations were available.

Regarding raubasine, a study in rats was noted in which administration by gavage at doses of 0, 5, 10, 20 and 40 mg/kg bw/day for 24 weeks did not produce any effect on body weight, haematology and histopathology.

No *in vitro* data on genotoxicity studies of yohimbe bark, its preparations or of yohimbine are available.

An *in vivo* genotoxicity assay in germ cells of male mice was performed after 90 days of treatment with an aqueous suspension yohimbe bark powder (yohimbine content not specified). In the same study, a number of parameters of male fertility were also measured. The Panel, however, had reservations about this study and therefore considered that no conclusions could be drawn concerning the genotoxicity and reproductive toxicity of yohimbe bark.

Raubasine was negative in the SOS chromotest in *E. coli* and did not induce gene conversion, crossing-over or reverse mutations in the yeast diploid strain XS2316.

No clinical studies investigating effects of yohimbe bark or its preparations are available. Therefore, evidence coming from studies on yohimbine and raubasine was considered. No human data were found for the other alkaloids present in yohimbe bark.

A published case report describing a hypertensive crisis following intake of an herbal product containing yohimbe bark for the treatment of impotence was noted and is suggestive of possible severe adverse effects of yohimbine. Based on the information provided in this single case report, it is not possible to ascertain the frequency of occurrence.

Human data encompass several case reports with yohimbine intoxications for which severe symptoms (hypertensive crisis, manic symptoms, anxiety, agitation, loss of consciousness) have been described.

Adverse effects listed in the summary of product characteristics for medicinal products containing yohimbine are: headache, nausea, increased urinary urge; insomnia, anxiety, restlessness, irritability (common); increase of blood pressure and pulse rate, palpitation, dizziness, vomiting, anorexia, gastric complaints, diarrhoea, flush, sweating, shivering, allergic reactions, nervousness (uncommon); hypotension, tremor, bronchospasm, dysuria, decreased urge, genital pains, exanthema (very rare).

Several studies in healthy volunteers have been carried out investigating various endpoints such as plasma concentrations of noradrenaline, glycerol and non-esterified fatty acids, blood pressure and heart rate, all increasing after administration of yohimbine. An antagonising effect on adrenaline-induced platelet aggregation was also shown. Yohimbine was associated with a dose-related increase in impulsive omission errors. In these studies in healthy volunteers 8 mg/person was the lowest dose showing antagonism on platelet aggregation without modifying blood pressure, standing heart rate, or plasma catecholamine or glucose concentrations. A dose of 12 mg yohimbine/person moderately but significantly accelerated supine heart rate.

According to a study in healthy volunteers, a single oral dose of 4 mg yohimbine/person (corresponding to 0.06 mg/kg bw) did not show effects on platelet aggregation and cardiovascular parameters as well as plasma catecholamines and glucose concentrations.

For medicinal products containing raubasine, a number of adverse effects are listed in the summary of product characteristics: dizziness, hypotension, sweating, flushing (rare); appearance of confusion, tachycardia, nausea, allergic reactions (occasionally).

In the human studies evaluated in the present opinion, raubasine did not show adverse effects in oral doses less than 10 mg per day (corresponding to approximately 0.15 mg/kg bw/day).

The Panel noted that the missing information include quantitative data on the composition and specifications of yohimbe bark and its preparations used in food and food supplements covering other alkaloids besides yohimbine, data on the bioavailability of active ingredients from the yohimbe bark extract and data on the toxicity of well specified individual preparations of yohimbe bark and the major yohimbe bark alkaloids, especially regarding subchronic toxicity, genotoxicity and reproductive toxicity.

The Panel concluded that according to the Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009) yohimbe bark and its preparations belong to the category of botanicals/botanical preparations for which the available data are not sufficient to conclude on their safety or possible health based guidance values (safety assessment based on available knowledge (Level A) revealed need for further data).

Furthermore the Panel concluded that based on the information on the use of yohimbe bark and its preparations in food supplements, estimated exposure to yohimbine could be similar to or higher than that at which effects were reported from the use of yohimbine in medicinal products.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The German Authorities have raised concerns regarding a potential risk to consumers linked with the consumption of foods containing Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille) and preparations made from them on the basis of a risk assessment report by the German Federal Institute for Risk Assessment (BfR) on Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille). The BfR risk assessment report refers to the use of yohimbe bark extract to treat sexual dysfunction and erectile problems and yohimbine as a weight-loss and performance enhancement drug for bodybuilders. The report concludes that "an assessment of the risks of yohimbe bark and preparations made from it based on the available data at level A (EFSA SC, 2009) show that the use of yohimbe bark and preparations made from it may be harmful to human health, although there is scientific uncertainty on this matter".

Consequently, the Commission has initiated the procedure under Article 8 (2) of Regulation (EC) No 1925/2006[4] on the addition of vitamins and minerals and of certain other substances to foods, for Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille).

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[5], the European Commission asks EFSA to:

- Review the existing scientific data on the possible link between the intake of Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille) and a harmful effect on health.

- Provide advice on a tolerable upper intake level (UL) for Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille), for the general population, and as appropriate, for vulnerable subgroups of the population.

- In the absence of a tolerable upper intake level (UL), to provide advice on a daily intake of Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille) that does not give rise to concerns about harmful effects to health.

INTERPRETATION OF THE TERMS OF REFERENCE BY THE ANS PANEL

The Panel noted that the term "tolerable upper intake level (UL)" was used by EFSA so far only for nutrients, such as vitamins or minerals, to describe the maximum level of total chronic daily intake judged to be unlikely to pose a risk of adverse health effects to humans. The Panel considered that the use of this term may not be appropriate for botanicals[6] and botanical preparations[7] being constituents of food supplements or other food products, especially in cases where the botanicals/botanical preparations or their main components have known medical uses based on scientifically established pharmacological properties and/or where the botanicals/ botanical preparations cannot be regarded as a component of the normal diet. Using the term "tolerable upper intake level (UL)" for botanicals and botanical preparations could lead to the misinterpretation that they could play a similar role in human nutrition as minerals and vitamins, which differ from them *inter alia* in being in general constituents of the normal diet and in being in many cases essential.

[4] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26-38.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures on matters of food safety. OJ L 31, 1.2.2002, p. 1-24.

[6] This includes all botanical materials (e.g. whole, fragmented or cut plants, plant parts, algae, fungi and lichens) (EFSA SC, 2009).

[7] This includes all preparations obtained from botanicals by various processes (e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation) (EFSA SC, 2009)

ASSESSMENT

1. Introduction

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) was asked to provide a scientific opinion on the safety of Yohimbe (*Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille) and preparations made from them when used in food, e.g. in the form of food supplements.

The evaluation is based on the published scientific literature as well as monographs and risk assessment reports by national and international authorities, which are available for *P. yohimbe* and their preparations and alkaloids, regarding food or drug use.

Concerns have been raised regarding a potential risk to consumers associated with the use of yohimbe bark or extracts thereof to treat sexual dysfunction and erectile problems and yohimbine as a weight-loss and performance enhancement drug for bodybuilders (BfR, 2012).

This risk assessment is carried out in the framework of the procedure under Article 8 (2) of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods, for Yohimbe initiated by the European Commission. Article 8 (2) of regulation (EC) No 1925/2006 is referring to a possible prohibition, restriction or Community scrutiny of a substance or ingredient by placement in Annex III, Part A, B or C of this regulation.

The risk assessment is carried out according to the EFSA Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009).

2. Technical data

2.1. Identity and nature of source material

Scientific (Latin) name	Family: *Rubiaceae* (Bedstraw family) Tribe*: Naucleeae* Genus: *Pausinystalia* L. Species: *Pausinystalia yohimbe* (K. Schumann) Pierre ex Beille
Synonyms	*Pausinystalia johimbe*, *Corynanthe yohimbe*, *Corynanthe johimbi*, *Corynanthe yohimbi*
Common names	Yohimbe, Johimbe, Liebesbaum, Lustholz, Potenzbaum
Part used	Bark (Yohimbehe cortex, Cortex Yohimbehe)
Geographical origin	Tropical West Africa (Cameroon, Congo, Gabon, Equatorial Guinea, Nigeria)
Growth and harvesting conditions	Gathering from wild plants mostly in Cameroon. No commercial plantations currently exist, although recent experiments have shown that clona propagation using shoots or general seed propagation is possible (Sunderland et al., 1999).

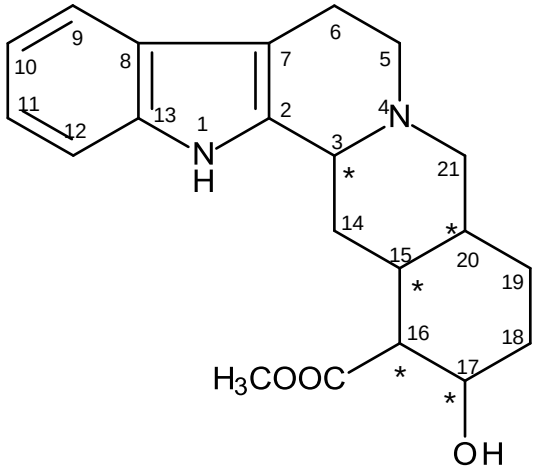
Information on the identity of the plant was taken from the following references: Kuhlmann, 1999; Blaschek et al., 2006; Wink et al., 2008; ACS, 2008, online; USDA ARS, online.

Yohimbe bark consists of dried bark of the trunk and branches of *P. yohimbe* (Expanded Commission E, online). The dried bark is marketed as flattened or slightly quilled pieces 75 cm long and 4-8 mm thick, with an external corky gray-brown layer covered with isolated lichens. In this form the bark

shows numerous longitudinal and transverse fissures that are uniform yellowish-brown with short, soft fibres like rough velvet (Betz et al., 1995).

2.2. Chemical composition

Data on the chemical composition of the bark are scarce and mostly refer to the biologically relevant indole alkaloids, the major one being yohimbine. These compounds feature a pentacyclic ring system with two nitrogen atoms and five chiral carbon atoms: C3; C15; C16; C17 and C20 (Figure 1) (Le Hir et al., 1953). Other reported components of the yohimbe bark are tannins (Gruenwald et al. 2007).



Legend: Chiral carbon atoms are indicated with an asterisk (*)

Figure 1: General structural formula of yohimbine stereoisomers

The configuration at C15 is always S[8] and yohimbine and its stereoisomers are broadly divided into four groups, namely: normal, pseudo, allo, and epiallo depending on the configurations at C3 and C20. They are further subdivided depending on the configurations of the C16 and C17 substituents (Chamala, 2010) as shown in Table 1.

Table 1: Classification and relative configuration of yohimbine and its stereoisomers based on Chamala, 2010.

Series	C(3)	C(20)	C(16)	C(17)	Alkaloid
normal	S	R	R	S	yohimbine[(a)]
			S	S	corynanthine[(a)]
			R	R	β-yohimbine[(a)]
pseudo	R	R	R	S	pseudoyohimbine[(a)]
			S	S	3-*epi*-corynanthine
			R	R	3-*epi*-β-yohimbine
allo	S	S	S	S	α-yohimbine[(a)]
			R	S	alloyohimbine[(a)]
epiallo	R	S	S	S	3-*epi*-α-yohimbine

[8] S and R are designations for absolute configuration, i.e. spatial arrangement of the substituent directly attached to the chiral centre (atom in a molecule that is bonded to four different chemical species) according to the Cahn-Ingold-Prelog priority rules.

	R	S	3-*epi*-alloyohimbine

(a): Alkaloids identified in yohimbe bark

Alkaloid content data vary, depending e.g. on the age of the plant, the height at which the bark is collected and analytical method used (Zanolari et al., 2003; Blaschek et al., 2006).

According to a number of investigations, the total alkaloid content of the bark is reported to be in the range of 2–61 mg/g (Brandt, 1922; Madaus, 1976; Betz et al., 1995; Blaschek et al., 2006; Gruenwald et al. 2007). Another source defines that yohimbe bark as a herbal drug should contain from 30 to 150 mg/g monoterpene indole alkaloids of the yohimbe bark type (Wink et al., 2008). For the extract, the content of 95–105 mg/g of total alkaloids, calculated as yohimbine, is described in the pharmaceutical literature (Blaschek et al., 2006).

The main alkaloid of the bark is yohimbine (Table 2). The other alkaloids are primarily yohimbine stereoisomers or derivatives thereof (Table 2) (Brandt, 1922; Duke, 1992; Tam et al., 2001; Blaschek et al., 2006).

The content of yohimbine in the bark is given as 7–115 mg/g and is usually around 10 mg/g (Le Hir et al., 1953; Betz et al., 1995; Zanolari et al., 2003; Blaschek et al., 2006; Chen et al., 2008). Zanolari et al. (2003) reported the yohimbine content in yohimbe bark of 13.03 ± 0.14 mg/g obtained by high performance liquid chromatography (HPLC)-ultraviolet (UV) method and 54.2 ± 1.5 mg/g obtained by HPLC-atmospheric pressure chemical ionisation (APCI)/mass spectrometry (MS) method and 115.1 mg/g obtained by HPLC-electrospray ionisation (ESI)/MS.

In the article by Chen et al. (2008) a sample of yohimbe bark (not further specified) was analysed by two different methods to give a yohimbine content of 11.7 mg/g when analysed by non-aqueous capillary electrophoresis (NACE) and 11.1 mg/g as analysed by gas chromatography (GC)-MS.

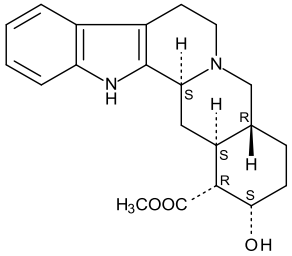
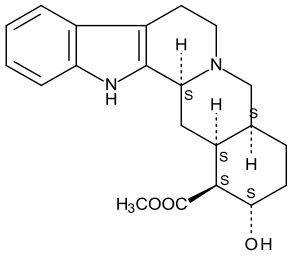
Other authors (Raman et al., 2013) found the content of yohimbine in the bark using ultra performance liquid chromatography (UPLC)-UV-MS to be in the range of 1 to 9.1 mg/g in various samples.

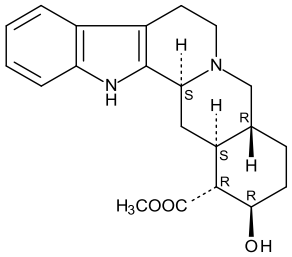
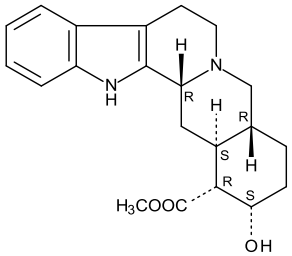
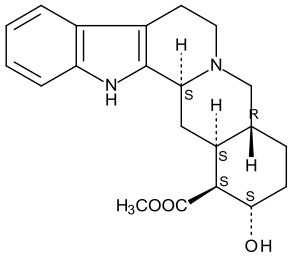
According to Zanolari et al. (2003) the values reported for yohimbine content may depend largely on the method used.

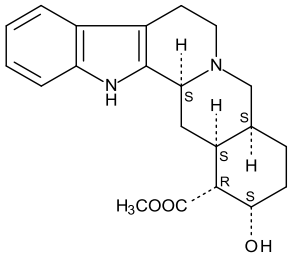
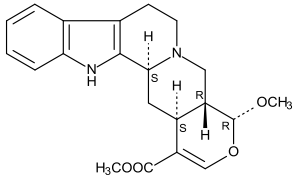
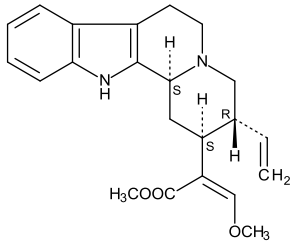
Yohimbine is very soluble in alcohol and sparingly soluble in water (NTP, 1997; Blaschek et al., 2006).

The presence of yohimbine and its stereoisomers has also been reported in the bark of the following plants: *Rauwolfia serpentina* (L.) Benth (Indian snakeroot), *Aspidosperma quebracho-blanco* Schltdl. (Quebracho), *Pseudocinchonia africans* Aug. Chev., *Coryanthe paniculata* Welw. and *Pausinystalia angolensis* Wernham and *Rauwolfia* spp. (Hajonides van der Meulen and van der Kerk, 1964; Chamala, 2010; Expanded Commission E, online).

Table 2: Main yohimbe bark alkaloids and relative synonyms, CAS numbers, molecular formula and molecular weight, structural formulas and reported levels.

Name	CAS Registry Number	Synonyms[(a)]	Molecular formula and molecular weight	Structural formula[(a)]	Content mg/g (analytical method)	Reference
yohimbine	146-48-5	(+)-yohimbine; aphrodine; corynine; quebrachine; yohimban-16α-carboxylic acid, 17α-hydroxy-, methyl ester, yohimbic acid methyl ester	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		8 (TLC on Al oxide) traces (TLC on Al oxide)	Le Hir et al., 1953
					11.5 22.4	Hajonides Van Der Meulen and Van Der Kerk, 1964
					7.089 (GC-NPD)	Betz et al., 1995
					1 - 9.1 (UPLC-UV/MS)	Raman et al., 2013
					13.03 (HPLC-UV) 54.2 (HPLC-APCI/MS) 115.1 (HPLC-ESI-MS	Zanolari, 2003
					11.7 (NACE) 11.1 (GC-MS)	Chen et al., 2008
					13.95 (UHPLC/UV/MS)	Sun and Chen, 2012
α-yohimbine	131-03-3	methyl (16β,17α,20α)-17-hydroxyyohimban-16-carboxylate; corynanthidine; isoyohimbine; mesoyohimbine; rauwolscine	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		traces (TLC on Al oxide)	Le Hir et al., 1953
					4.6 3.9	Hajonides Van Der Meulen and Van Der Kerk, 1964
					1.62 (NACE) 1.535 (GC-MS)	Chen et al., 2008

Name	CAS Registry Number	Synonyms[(a)]	Molecular formula and molecular weight	Structural formula[(a)]	Content mg/g (analytical method)	Reference
β-yohimbine	549-84-8	methyl (16α,17β)-17-hydroxyyohimban-16-carboxylate; amsonine	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		0.3 (TLC on Al oxide) traces (TLC on Al oxide)	Le Hir et al., 1953
					1.75 (NACE) 1.67 (GC-MS)	Chen et al., 2008
pseudoyohimbine	84-37-7	yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester, (3β,16α,17α); ψ-yohimbine	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		0.4 (TLC on Al oxide) 2.3 (TLC on Al oxide)	Le Hir et al., 1953
					3.6 0.2	Hajonides Van Der Meulen and Van Der Kerk, 1964
corynanthine	483-10-3	methyl (16β,17α)-17-hydroxyyohimban-16-carboxylate; rauhimbine	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		Identified but no quantification data on the single alkaloid	Blaschek et al., 2006

Name	CAS Registry Number	Synonyms[(a)]	Molecular formula and molecular weight	Structural formula[(a)]	Content mg/g (analytical method)	Reference
alloyohimbine	522-94-1	yohimban-16-carboxylic acid, 17-hydroxy-, methyl ester, (16α,17α,20α)-; alloyohimbine (6CI, 7CI)	$C_{21}H_{26}N_2O_3$ 354.44 g/mol		0.8 (TLC on Al oxide)	Le Hir et al., 1953
raubasine	483-04-5	δ-yohimbine; ajmalicine; tetrahydroserpentine; vincaine	$C_{21}H_{24}N_2O_3$ 352.43 g/mol		0.41 (NACE) 0.39 (GC-MS)	Chen et al., 2008
corynantheine	18904-54-6	17,18-secoyohimban-16-carboxylic acid, 16,17,18,19-tetradehydro-17-methoxy-, methyl ester, (E)- (8CI); corynan-16-carboxylic acid, 16,17,18,19-tetradehydro-17-methoxy-, methyl ester, (16E)-	$C_{22}H_{26}N_2O_3$ 366.45 g/mol		0.056 (NACE) 0.053 (GC-MS)	Chen et al., 2008

(a): From SciFinder, online

2.2.1. Biosynthesis of the yohimbe alkaloids

Yohimbine and its isomers are monoterpenoid-derived indole alkaloids formed from the initial condensation of tryptamine with secologanin in the presence of strictosidine synthase to form strictosidine. The tryptamine portion of the alkaloid is derived from the decarboxylation of tryptophan with tryptophan decarboxylase enzyme. Strictosidine, after deglycosylation with glycosidase, through a series of reactive intermediates forms 4,21-dehydrocorynantheine aldehyde which undergoes isomerisation and reduction to afford yohimbine. Probable biosynthetic pathway for the formation of yohimbine alkaloids is presented in Figure 2 (Chamala, 2010).

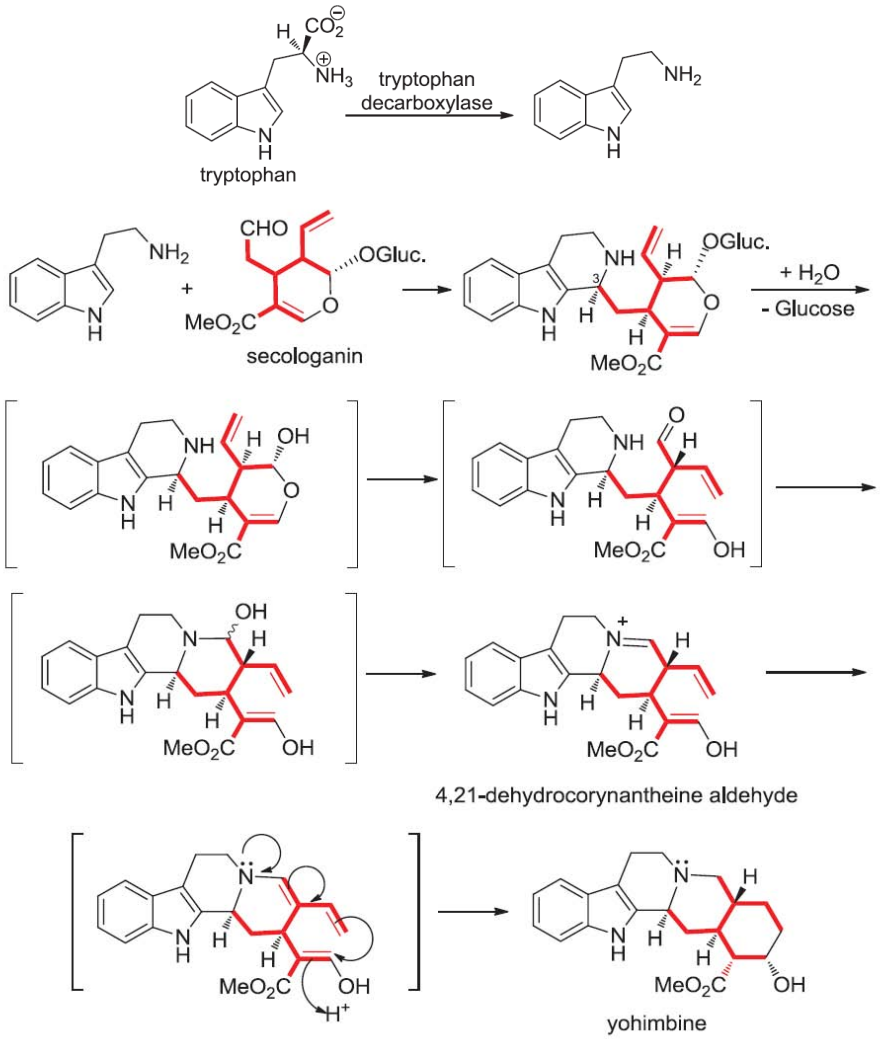


Figure 2: Probable biosynthetic pathway for the formation of yohimbine from Chamala, 2010.

2.3. Specifications

No specifications for yohimbe bark or its preparations such as extracts for the use in food are known.

The European Pharmacopoeia (2011) contains specifications for yohimbine hydrochloride (CAS No. 65-19-0).

Yohimbine hydrochloride is sparingly soluble in water and practically insoluble in ethanol (96 %) (European Pharmacopoeia, 2011).

2.4. Manufacturing process

Dried bark from the twigs and trunk of the Yohimbe tree is used in its entirety, cut up or ground into powder to be used as a drug. Yohimbe bark extracts are available (CAS: 85117-22-2) (Blaschek et al., 2006, SciFinder, online). There is no information on standardisation of the extracts for use in food with regard to the ratio of extracted material to starting material, extraction solvent, content of biologically active ingredients. Yohimbine, the main component of the bark, can either be obtained from the bark or chemically synthesised (Blaschek et al., 2006; Chamala, 2010).

The isomers of Yohimbine may also be produced synthetically (Chamala, 2010).

2.5. Methods of analysis in food

There are no official inter-laboratory validated methods for determining the levels of yohimbine and accompanying alkaloids in food.

In a congress abstract light and scanning electron microscopy studies of yohimbe bark were presented. Micromorphology and arrangement of fibres, radially arranged cork cells with thick walls, presence of numerous idioblasts containing sand crystals of calcium oxalate are diagnostic features. A few variations in the structure of fibres were observed and are reported. UPLC-UV-MS analysis was conducted and the yohimbine content was found to be in the range of 0.1-0.91 % for various samples (Raman et al., 2013).

A single-laboratory validated method for determination of yohimbine in commercial products using GC with nitrogen-phosphorous detector (NPD) has been described by Betz et al. (1995). The limit of quantitation (LOQ) for this analysis was 0.1 mg/kg, and recoveries were 80 % for liquid products, 65-70 % for caplets and capsules, and 40 % for fortified protein supplements.

Zanolari et al. (2003) developed methods based on HPLC and UV and MS techniques with APCI and ESI for determination of yohimbine in yohimbe bark and in commercial aphrodisiacs. According to the validation results, in the absence of certain yohimbine isomers (such as corynanthine), both HPLC-APCI/MS and HPLC-ESI/MS appeared to be very selective and robust methods with a sensitivity 20 times greater than the HPLC-UV method (limit of detection (LOD) = 0.03 ng; LOQ = 0.1 ng). The advantages of the HPLC-UV technique are the greater range of linearity and the possibility of quantifying small quantities of yohimbine isomers (i.e. less than 1 % of the total yohimbine amount).

Validated GC-MS and NACE methods for analysis of yohimbe alkaloids in the bark of *Rubiaceae* species were described by Chen et al. (2008). The recovery of yohimbine was 91.2-94.0 % with relative standard deviation (RSD) 1.4-4.3 %. The LOD for yohimbine was 0.6 µg/ml by GC-MS and 1.0 µg/ml by NACE, respectively.

2.6. Stability of the botanicals or botanical preparations used as ingredients in food supplements and reaction and fate in food

No data are available on the stability of yohimbe bark or preparations such as extracts thereof in food.

Yohimbine hydrochloride should be kept in air tight containers, protected from light (European Pharmacopoeia 7.0, 2011).

2.7. Uses and use levels (including products marketed via internet)

2.7.1. Common foods

The European Herbal Infusions Association (EHIA) declared that *P. yohimbe* is not used, as a plant or part of plant, by the European industry for herbal and fruit infusions (Letter from EHIA, personal communication, April 2013).

There is no indication that yohimbe bark or its preparations are a component of common food in Europe.

2.7.2. Food supplements

Dietary supplements of yohimbe bark are commercially available to improve sexual performance and enhancement of sexual satisfaction and for weight loss purposes also in combination with other substances (e.g. caffeine). According to a survey conducted among its members, the European Responsible Nutrition Alliance (ERNA) declared that yohimbe bark and its preparations are not used in food supplements and other food products and as a result of the current situation there has been no interest in data demonstrating its safety for food use (Letter from ERNA, personal communication, April 2013).

Thus, the Panel considered that generally these products may not be marketed in Europe but that at present they can be easily purchased through the internet.

Determination of yohimbine in yohimbe bark and related dietary supplements has been carried out in two studies from the United States and reported in Table 3.

Sun and Chen (2012) analysed 13 yohimbe commercial dietary supplement samples by means of an ultra high-performance liquid chromatography (UHPLC) method whereas information on another 11 products are reported by Zanolari et al. (2003). A method based on an HPLC-UV-MS technique was used in the latter case and these results are likely to be overestimated by the fact that this method of analysis measured the combined amount of yohimbine and corynanthine from yohimbe bark extract.

Both studies show that the yohimbine content in commercial dietary supplements varies greatly. In addition, yohimbine content was not consistent with the amount claimed on the label for most of the dietary supplements analysed. Yohimbine content was declared in only two products considered by Zanolari et al. (2003) and these values did not correspond with the quantities analytically determined (5.8 vs. 4 mg/kg and 1.24 vs. 2.7 mg/kg, respectively). Sun and Chen (2012) noted that only one solid sample agreed with the label claim, two samples contained more yohimbe bark compared to the label claims (140 % and 180 %, respectively), the rest ranged from 6 % to 50 % of the label claims except one which did not have any detectable amount of yohimbine. The two liquid samples contained about 3 % and 17 % of the label claims, respectively. Consequently, information on the declared content of yohimbine or yohimbe bark in food supplements, reported on the label or on the commercial web page, is not considered reliable and cannot be used for the assessment of exposure.

A study conducted by Betz et al. (1995) showed that extracts contain a maximum of 7 % of the yohimbine detectable in the bark, with the majority of products having a significantly lower to zero detectable yohimbine content. The authors explain this by the very high rate of dilution of the end-product and by watery extraction methods.

The Panel noted that quantitative data for alkaloids other than yohimbine in yohimbe bark containing food supplements are missing and would be specially needed for pharmacologically active substances such as raubasine[9].

[9] It should be noted that the terms raubasine and ajmalicine are synonyms indicating the same alkaloid. In this opinion the term raubasine has been preferentially used.

Table 3: Yohimbine in yohimbe bark and dietary supplements

Dietary supplement type	Yohimbine (analytically determined)		Max No of suggested servings per day	Content of yohimbe bark, extract or yohimbine as reported in the label (mg/serving)	Estimated exposure to yohimbine (mg/ kg bw/day)[a]		Reference
	mg/g or mg/ml	mg/serving			Minimum	Maximum	
AHP[b] bark	13.95 ± 0.1	- -	Not available	-	-		Sun and Chen, 2012
Capsule	0.96 ± 0.0	0.52 ± 0.05	Not available	-	0.01	0.03	Sun and Chen, 2012
	16.54 ± 0.2	9.93 ± 0.11	Not available	500	0.28	0.57	Sun and Chen, 2012
	5.49 ± 0.1	4.14 ± 0.06	Not available	750	0.12	0.24	Sun and Chen, 2012
	1.78 ± 0.0	1.59 ± 0.09	Not available	600	0.05	0.09	Sun and Chen, 2012
	NA[c]	0.50 ± 0.08	4	150 (Yohimbe)	0.03		Zanolari et al., 2003
	0.88 ± 0.0	1.09 ± 0.04	Not available	1200	0.03	0.06	Sun and Chen, 2012
	8.89 ± 0.1	5.33 ± 0.02	Not available	400	0.15	0.30	Sun and Chen, 2012
	NA[c]	9.52 ± 0.52	2	250 (extract)/5 (2 %)	0.27		Zanolari et al., 2003
	12.67 ± 0.0	3.91 ± 0.00	Not available	-	0.11	0.22	Sun and Chen, 2012
	NA[c]	0.59 ± 0.10	2	125 (bark)	0.02		Zanolari et al., 2003
	NA[c]	0.88 ± 0.16	4	Not specified	0.05		Zanolari et al., 2003
Liquid	2.4 ± 0.0	2.40 ± 0.01	Not available	1000	0.10		Sun and Chen, 2012
	0.14 ± 0.0	0.14 ± 0.01	Not available	333	0.01		Sun and Chen, 2012
	NA[c]	0.99 ± 0.18	3	NA[c]	0.04		Zanolari et al., 2003
Mass		2.33 ± 0.06	5	Not specified	0.17		Zanolari et al., 2003
Tablet	0.54 ± 0.0	0.68 ± 0.05	Not available	800	0.02	0.04	Sun and Chen, 2012
	0.15 ± 0.0	0.65 ± 0.00	Not available	250	0.02	0.04	Sun and Chen, 2012
	NA[c]	5.80 ± 1.10	4	200 (extract)/4 (2 %)	0.33		Zanolari et al., 2003
	NA[c]	1.24 ± 0.14	2	270 (extract)/2.7	0.04		Zanolari et al., 2003
	7.46 ± 0.0	18.8 ± 0.12	Not available	750	0.54	1.07	Sun and Chen, 2012
	0.51 ± 0.2	0.7 ± 0.00	Not available	100	0.02		Sun and Chen, 2012
	NA[c]	1.21 ± 0.18	2	125 (extract)/2.5 (2 %)	0.03		Zanolari et al., 2003
	NA[c]	0.53 ± 0.00	3	250 (extract)/5 (2 %)	0.02		Zanolari et al., 2003
	NA[c]	3.15 ± 0.34	4	NA[c]	0.18		Zanolari et al., 2003

a): minimum and maximum exposure to yohimbine have been estimated by multiplying the yohimbine content per serving, as analysed, by the minimum and maximum number of suggested servings per day for the same dietary supplement type, respectively. A body weight of 70 kg has been used to express the exposure results in mg/day per kg body weight

(b): American Herbal Pharmacopoeia

(c): Not available

2.7.3. Medicinal products

2.7.3.1. Use of yohimbe bark and its preparations

There is only sparse information available from older literature about the use of the herbal substance[10] or preparations thereof. Decoctions of the bark were used mainly in West Africa as an aphrodisiac to stimulate sexual desire and performance (Loewy, 1900; Madaus, 1976). It seems to have been used as a local anaesthetic, a mild stimulant to prevent drowsiness, a hallucinogen, a treatment for angina, a hypertensive, a general tonic, a treatment for intestinal worms, a performance enhancer for athletes, and to increase the clarity of singers' voices during long cultural festivals (Clark and Sunderland, 2004).

From old literature it could be found that medicinal products containing yohimbe bark or preparations thereof, including yohimbine as isolated substance (also as combination products) were on the European market for over 100 years (Arends and Zörnig, 1938).

In the EB6 (1953) the usage of the bark of *P. yohimbe* was mentioned. Commission E[11] (Blumenthal et al., 1998) did not recommend the usage of yohimbe bark because of insufficient proof of efficacy and the unforeseeable correlation between risk and benefit for the indications sexual disorders, as an aphrodisiac, for feebleness and exhaustion.

From data provided by 16 out of 30 European Economic Area (EEA) Member States during a recent survey conducted by the European Medicines Agency (EMA) it appears that no mono ingredient (traditional) herbal medicinal products containing herbal substances/preparations from *P. yohimbe* are authorised or registered in the EU (Letter from EMA, personal communication, April 2013).

2.7.3.2. Use of single alkaloids from yohimbe bark

Information on existing authorised medicinal products containing the individual alkaloids contained in the yohimbe bark have been gathered by the EMA from 16 EEA Member States and are summarised in Table 4. The table does not contain information on homeopathic products and on products not for oral use.

[10] In this opinion the term 'herbal substance' is used as defined in Directive 2001/83/EC, i.e.: "All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)".

[11] Commission E is a scientific expert committee for herbal medicinal products providing support to the German Federal Institute for Drugs and Medical Devices in drafting monographs for herbal preparations.

Table 4: Summary of information reported for the authorisation medicinal products for oral use containing yohimbine or raubasine as single ingredient.

Substance	Posology [(a)]		Therapeutic indications [(a)]	Contraindications and warnings [(a)]	Adverse effects [(a)]
	Single dose range	Daily dose range			
yohimbine HCl	5 mg (may be increased to 10 mg)	10-15 mg (may be increased to 30 mg) for at least 8 weeks	(psychogenic) erectile dysfunction; male climacterium or Disorders of the sexual potency, e.g. of the potentia coeundi; libido disorders; reduced reflex agitation of the lumbosacral mark; general and sexual-specific symptoms of the male climacterium. or supportive treatment of mild to moderate erectile dysfunction in the context of other therapeutic actions	Hypersensitivity to the active ingredient. Cardiac disorders (especially heart disease, tachycardic arrhythmia). Hypertension, hypotension. Greatly impaired kidney or liver function. Ulcer (stomach or intestine). Glaucoma. Psychiatric disorders, particularly mood disorders and anxiety. Concomitant use of central nervous acting drugs. There exist no adequate clinical experiences with treatment in women. It is also not possible to determine effects on a fetus during pregnancy. Not be used in women. Not indicated for treatment in patients less than 18 years. Warning: the oral intake of 200 mg yohimbine hydrochloride led to intoxication symptoms (e.g. with weakness, general paresthesia, loss of coordination and memory performance, epileptic seizures, headaches with dizziness, tremor, palpitations and anxiety, chest pain) The usage may lead to positive results in doping tests.	*Cardiac disorders* Uncommon: increase of blood pressure and pulse rate, palpitation Very rare: hypotension *Nervous system disorders* Common: headache Uncommon: dizziness Very rare: tremor *Respiratory, thoracic and mediastinal disorders* Very rare: bronchospasm *Gastrointestinal disorders* Common: nausea Uncommon: vomiting, anorexia, gastric complaints, diarrhoea *Renal and urinary disorders* Common: increased urge Very rare: dysuria, decreased urge, genital pains *Skin and subcutaneous tissue disorders* Uncommon: flush Very rare: exanthema *General disorders* Uncommon: sweating, shivering *Immune system disorders* Uncommon: allergic reactions
raubasine	10-20 mg	20-60 mg	Adjuvant in the treatment of peripheral arterial disorders	Hypersensitivity to the active substance. Serious heart disease. Haemorrhagic syndrome or intracranial hypertension. Uncompensated heart failure, valvular stenosis, significant reduction of the pulmonary circulatory bed, glaucoma. First three months of pregnancy. During or within two weeks after treatment with MAOIs	Rare: dizziness, hypotension, sweating, flushing Occasionally: appearance of confusion, tachycardia, nausea, allergic reactions In the case of heart disease or other general disorders may require discontinuation of therapy.

(a): As reported in the Summary of Product Characteristics of the authorised medicinal products.

2.8. Exposure

2.8.1. Exposure via food supplements

Exposure to yohimbine from food supplements has been estimated by multiplying the number of suggested servings per day by the yohimbine content per serving, as analysed by Zanolari et al. (2003) and Sun and Chen (2012) as reported in Table 3. Due to the fact that the number of suggested servings per day was only available for the food supplements analysed by Zanolari et al. (2003) the minimum and maximum serving, within those reported for the same dietary supplement type, was used in the other cases. For example, in the case of tablets the number of servings per day ranges from 2 to 4. These two figures were used for all dietary supplements served as tablets to estimate minimum and maximum acute exposure to yohimbine, respectively. As suggested by the Scientific Committee of EFSA (EFSA SC, 2012) a body weight of 70 kg has been used in this opinion as the default value to express the exposure results in mg/kg bw/day. Maximum daily exposure to yohimbine was estimated as up to 1.07 mg/kg bw, corresponding to 75 mg/person for a 70 kg adult consuming in a day 4 tablets containing 18.8 mg of yohimbine each (the highest measured value reported in the literature).

2.8.2. Other sources of exposure (medicinal products)

As shown in Table 4, the single dose and the daily dose of yohimbine in the form of the hydrochloride is 5–10 mg per single dose and 10–30 mg per daily dose, corresponding to approximately 0.14 to 0.43 mg/kg bw/day (calculated using a default value of 70 kg bw according to EFSA SC, 2012).

2.9. Information on existing authorisations, evaluations and regulations

P. yohimbe is listed in the EFSA Compendium of Botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements (EFSA, 2012).

No records for yohimbe bark and its preparations can be found in the EU Register on nutrition and health claims (EC, online).

The EMA has confirmed that no monographs or assessment reports on safety/efficacy are available or currently expected from the Committee on Herbal Medicinal Products (HMPC) and that yohimbe bark is not on the HMPC priority list. It is important to note that one of the reasons for the lack of priority is due to concerns about the safety and known risks associated with the content and use of these substances. The HMPC does not normally prioritise substances with a predictable negative outcome of the benefit-risk assessment in line with provisions of Directive 2001/83/EC[12] for traditional herbal medicinal products, which includes the provision to establish a plausible and safe medicinal use under specified conditions suitable for self-medication without medical supervision. (Letter from EMA, personal communication, April 2013).

P. yohimbe appears on the former European Commission's Committee for Proprietary Medicinal Products list of Herbal drugs with serious risks, dated 1992[13] as "*Drugs with toxic principles, where a more detailed discussion concerning the benefit/risk ratio is necessary"* (alkaloid containing plants requiring a benefit risk assessment during the revision)". In a statement from 2005, the HMPC provided clarification on how this list should be read today (EMA, 2005).

[12] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ L 311, 28.11.2011, p.67-128.
[13] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/09/WC500111303.pdf

A response of 16 EEA Member States to EMA's request for information indicates that currently there are no medicinal products containing yohimbe bark or extracts thereof registered in these countries. Few Member States have registered medicinal products containing yohimbine for oral use (tablets). There is a single registered medicinal product containing raubasine in Italy (peroral drops or coated pills).

In Ireland, the use of Yohimbe is not permitted in Traditional Herbal Medicinal Products, as it would be controlled as a prescription medicine under the terms of the Medicinal Products Regulations.

The United Kingdom does not consider any products containing *P. yohimbe* or yohimbine to be classified as foods. In the UK the sale and supply of botanicals containing *P. yohimbe* are controlled under the Medicines (Retail Sale or Supply of Herbal Plants Remedies) Order 1977 SI 2130.

The use of the bark of *P. yohimbe* is prohibited in the production of foods in the Czech Republic.[14]

The use of *P. yohimbe* and its alkaloids is not authorised as food or food supplements in Belgium (Royal Decree of 29 August 1997).

Food supplements with *P. yohimbe* herbal substance/herbal preparations are not allowed on the Dutch market based on the Warenwetbesluit Kruidenpreparaten (Letter from EMA, personal communication, April 2013).

The Austrian food codex (*Codex Alimentarius Austriacus*, Österreichisches Lebensmittelbuch) includes the species *P. johimbe* in a list of plants not to be used for the production of herbal teas.[15]

In Germany, yohimbe bark is the subject of a negative (unapproved) monograph in the Commission E due to lack of data and safety concern (Blumenthal et al., 1998).

The Danish Drogelisten lists Yohimbe (under the synonym *Corynanthe johimbe* K. Schum) as a plant that is unacceptable as food regardless of amount (DTU, online).

Health Canada's drugs directorate policy on herbals used as non-medicinal ingredients in non-prescription drugs in human use includes Yohimbe (*Corynanthe yohimbe*, *P. yohimbe*) in the list of herbs unacceptable as non-medicinal ingredients in oral use products (Health Canada, 1995, online).

Health Canada's guidance document Drugs Currently Regulated as New Drugs includes yohimbine as aphrodisiac in The New Drugs List (Health Canada, 2012a, online).

Yohimbine or its salts are included in the draft of the proposed Prescription Drug List of Health Canada for both human and veterinary use (Health Canada, 2012b, online).

The Australia New Zealand Food Standards Code lists in the Standard 1.4.4 (Prohibited and Restricted Plants and Fungi) the species *P. yohimbe*, syn. *Coryanthe yohimbe* (yohimbe) in the schedule of prohibited plants and fungi, stating that these plants or fungi, or a part or a derivative of a plant or fungus, or any substance derived therefrom, must not be intentionally added to food or offered for sale as food.[16]

[14] 225. Vyhláška, kterou se stanoví požadavky na doplňky stravy a na obohacování potravin. Sbírka Zákonů Česká Republika 30.06.2008, Částka 71, p. 3230-3242.
See the regulation: vyhláška č. 225/2008 Sb. (Annex 4). www.mvcr.cz/soubor/sb071-08-pdf.aspx

[15] Österreichisches Lebensmittelbuch, Codexkapitel B 31 – Tee und teeähnliche Erzeugnisse, Anhang II – Liste der für die Herstellung teeähnlicher Erzeugnisse nicht verwendeter Pflanzen bzw. Pflanzenteile.

[16] Australia New Zealand Food Standards Code. Standard 1.4.4 Prohibited and Restricted Plants and Fungi. Federal Register of Legislative Instruments F2011C00580. Issue 124. Prepared on 11.07.2011.

Yohimbine and preparations containing yohimbine are listed as aphrodisiacs in a schedule of goods the importation of which is prohibited by the Customs (Prohibited Imports) Regulations 1956 of Australia.[17]

3. Biological and toxicological data

In the following sections, priority will be given to the toxicological studies investigating yohimbe bark and its preparations. Since yohimbine is the main alkaloid of yohimbe bark and the only alkaloid for which occurrence has been measured in food supplements containing yohimbe bark, studies with yohimbine in particular are also considered.

The Panel noted that other alkaloids could be present in yohimbe bark containing food supplements and given the known pharmacological properties of raubasine and its possible occurrence, also considered these data.

The Panel noted that stereoisomers of yohimbine occurring in the bark may have biological activity (Tanaka and Starke, 1980; Timmermans et al., 1981, Chamala, 2010), however no relevant *in vivo* data were available for assessment.

3.1. Absorption, distribution, metabolism and excretion (ADME)

3.1.1. Yohimbe bark and its preparations

There are no available data describing the ADME of yohimbe alkaloids after administration of yohimbe bark preparations such as extracts.

3.1.2. Yohimbine and other yohimbe bark alkaloids (raubasine and corynanthine)

***In vitro* study**

The absorption of yohimbine, raubasine and corynanthine as chemical constituents of some traditional Chinese medicines was investigated in an *in vitro* study using Caco-2 cell monolayers as a human intestinal epithelial cell model (Ma and Yang, 2008). The permeability of the three alkaloids was studied measuring their influx from apical side to basolateral side and the efflux from basolateral side to apical side and their correlation with the partition coefficient. The three alkaloids were measured by high performance liquid chromatography coupled with UV detection. The ratio of efflux to influx permeability of yohimbine, raubasine and corynanthine were 1.29, 0.54 and 1.28, respectively. According to the authors, these compounds can be transported and absorbed across the human Caco-2 cells monolayers, and the oil-water partition coefficient would play key roles in the transport and absorption of the three alkaloids.

Animal studies

The distribution and metabolism of yohimbine was investigated in mice receiving an intraperitoneal (i.p.) administration of yohimbine tritiated on methyl (10 mg/kg bw, 250 µCi) (Ho et al., 1971). The labelling penetrated rapidly the brain (10 minutes after dosing). There was no marked differential distribution of tritium in the different topographical regions of the brain. Twenty-four hours after

[17] Customs (Prohibited Imports) Regulations 1956 Statutory Rules 1956 No. 90 as amended. Prepared by the Office of Parliamentary Counsel. Federal Register of Legislative Instruments F2013C00003. Prepared 01.01.2013

injection most of the radioactivity was located in brain, kidneys, liver, intestine and muscle. At least two radioactive unidentified metabolites were found in the extracts of liver and spleen or in urine.

The concentration of yohimbine in serum and brain of conscious Sprague-Dawley rats at various times after intravenous (i.v.) injection of 1 mg/kg bw of yohimbine was measured using HPLC with fluorescence detection (Hubbard et al., 1988). The serum concentration-time profile of yohimbine was biphasic with a rapid distribution phase (half-time approximately 3 minutes) followed by a very slow elimination phase (half-time 16.3 hours). The clearance of yohimbine was 11 ml/h/kg, and the volume of distribution was 259 ml/kg. Increasing doses (0.3, 1 and 3 mg/kg bw, i.v.) of yohimbine produced non-linear increases in serum yohimbine concentration. Yohimbine entered the brain rapidly (5 000 ng/g at 5 min after dosing) and had a slow elimination rate from the brain (half-time of 7.7 hours). In contrast to serum yohimbine concentration, in the brain increasing doses of yohimbine (0.3, 1 and 3 mg/kg bw, i.v.) produced linear increases in yohimbine concentration, a phenomenon which is consistent with concentration-dependent binding of yohimbine to plasma proteins.

There were no identified data of ADME in animals following oral administration of yohimbine.

Human studies

The kinetic disposition of yohimbine following oral administration was investigated in eight young male subjects receiving a single oral dose of 10 mg yohimbine hydrochloride (Owen et al., 1987). Results from this study showed that yohimbine was very rapidly absorbed (half-time 11 minutes) in the systemic circulation and rapidly eliminated from the plasma (half-time 36 minutes). The authors reported that the clearance of yohimbine from plasma was constant over approximately 10 elimination half-lives, thus suggesting that distribution into a second distinct pharmacokinetic compartment was not responsible for the rapid decline in plasma yohimbine levels. It was also reported that yohimbine did not undergo direct urinary excretion, as less than 1 % of the dose was recovered as parent compound in the urine within 24 hours. These results suggest that yohimbine is eliminated primarily through metabolism.

Pharmacokinetic profiles were determined in seven healthy young male subjects following single oral or i.v. doses of 10 mg of yohimbine hydrochloride (Guthrie et al., 1990). The results from this study showed that yohimbine was rapidly eliminated (half-time of 35 minutes and 40 minutes following oral and i.v. administration, respectively). Following i.v. administration, the data fit a two-compartment pharmacokinetic model, with a very rapid distribution phase (half-time approximately 6 min). Both the oral and the intravenous yohimbine clearance values were high, but oral clearance values were much higher (mean 9.77 ml/min/kg i.v. versus 55.9 ml/min/kg oral). The data on the oral bioavailability showed great variability, ranging from 7 % to 87 % (mean value was 33 %). According to the authors, the incomplete oral bioavailability of yohimbine may reflect either incomplete absorption from the gastrointestinal tract or a hepatic first pass effect. In conclusion, although yohimbine is rapidly absorbed when given orally, the bioavailability is quite variable.

Le Verge et al. (1992) demonstrated the existence of at least two metabolites of yohimbine in plasma or urine of orally or i.v. treated humans. The method used, a normal-phase HPLC combined to NMR and mass spectral analyses, allowed the identification of yohimbine and its hydroxylated metabolites, 10-hydroxyyohimbine and 11-hydroxyyohimbine, in biological samples. The extraction yields of yohimbine, 10-hydroxyyohimbine and 11-hydroxyyohimbine from plasma were 91.8, 45.3 and 17.8 %, respectively, and their respective within-day reproducibility were 3.8, 1.4 and 5.9 %. The between-day reproducibility for yohimbine at the concentrations of 1 and 10 ng/ml were 8.9 and 6.4 %, respectively. The accuracy of the method for yohimbine at concentrations of 1 and 10 ng/ml was 5.1 and 2.3 %, respectively. The limits of quantification of yohimbine, 10-hydroxyyohimbine and 11-hydroxyyohimbine were 0.1, 0.5 and 1 ng/ml, respectively.

The pharmacokinetics of yohimbine and its sympatho-adrenal effects as an α_2-adrenergic receptor antagonist were studied in 13 young, healthy, male volunteers after an intravenous bolus dose of 0.25

or 0.5 mg/kg bw (Hedner et al., 1992). The results showed that yohimbine was rapidly distributed (half-time ranging from 0.4 and 18 minutes). The elimination half-time had greater variability, ranging from 15 minutes to 2.5 h. The average volume of distribution (Vss) was 74 l, (ranging from 26 to 127 l). As previously observed, only 0.5 to 1 % of unchanged yohimbine was found in the urine, indicating that the major part of the drug was eliminated by hepatic clearance. Total plasma clearance was 117 l/h, which exceeded the hepatic plasma flow. The authors considered these findings as suggestive of the fact that yohimbine is a high extraction drug with considerable extra-hepatic metabolism. Fractional urine sampling revealed that 0.5–1% of unchanged yohimbine was excreted in urine in a biphasic manner. The data also suggested the existence of a slower elimination phase, with a half-time of 13 hours. With regard to the sympatho-adrenal effects of yohimbine, a three-fold increase in the plasma concentration of noradrenaline was reported 15 minutes after the yohimbine injection. Plasma adrenaline and neuropeptide Y (NPY)-like immunoreactivity remained unchanged. The plasma concentration-effect relationship of the changes in circulating noradrenaline followed counter-clockwise hysteresis. According to the authors, the results showed that the hyperadrenergic state elicited by therapeutic doses of yohimbine is due to an interaction with noradrenaline but not to release of adrenaline or NPY in man.

Berlan et al. (1993) investigated the α_2-adrenoreceptor antagonist properties of the two hydroxylated metabolites of yohimbine in man (10-hydroxyyohimbine and 11-hydroxyyohimbine) on the α_2-adrenoreceptors of human platelets and adipocytes. The effects observed were compared to those of yohimbine. Yohimbine and 11-hydroxyyohimbine exhibited similar α_2-adrenoreceptor affinity in biological studies i.e. inhibition of adrenaline-induced platelet aggregation and inhibition of antilipolysis induced by an α_2-adrenoreceptor agonist (UK14304) in adipocytes. Yohimbine and the two metabolites displaced a labelled selective α_2-adrenoreceptor antagonist (^{3}H-RX 821002) binding with equivalent affinities in platelet and adipocyte membranes with the following order of potency: yohimbine > 11-hydroxyyohimbine > 10-hydroxyyohimbine. However, when binding studies were carried out in binding buffer supplemented with 5 % albumin, the apparent affinity of yohimbine was reduced about 10-fold and was similar to that of 11-hydroxyyohimbine. Yohimbine and its metabolites were bound to different extents to plasma proteins, the bound fraction being 82 %, 43 % and 32 % respectively for yohimbine, 11-hydroxyyohimbine and 10-hydroxyyohimbine. These results show that the main hydroxylated metabolite of yohimbine in man (11-hydroxyyohimbine) possesses α_2-adrenoreceptor antagonist properties. According to the authors, the discrepancies found in binding studies (i.e. 10 fold lower affinity of 11-hydroxyyohimbine than yohimbine for α_2-adrenoreceptor antagonist properties) were attributable to the higher degree of binding of yohimbine to plasma protein.

A study was conducted to examine tolerability and pharmacodynamics of single doses of yohimbine in healthy volunteers using measures of mood, heart rate, blood pressure, and serum catecholamine levels (Grasing et al., 1996). Participants were given single oral doses of yohimbine hydrochloride (5.4, 10.8, 16.2 and 21.6 mg). Plasma concentrations of yohimbine, adrenaline, noradrenaline and 3-methoxy-4-hydroxyphenylethylene-glycol (MHPG) were quantified by means of HPLC. Yohimbine was well tolerated and rapidly absorbed and eliminated. Dose-related increases in the area under the concentration-time curve (AUC) were observed, associated with more pronounced effects on the parameters measured. Administration of yohimbine in the presence of a high fat meal diminished both the rate and extent of drug absorption. Significant inter-individual variability in the pharmacokinetic parameters of yohimbine was observed, with some individuals exhibiting greatly increased oral bioavailability of yohimbine. The results indicate that higher doses of yohimbine are both well tolerated and produce dose-related increases in AUC, which are associated with more pronounced autonomic effects.

Sturgil et al. (1997) determined the safety, pharmacodynamic response, and single- and multiple-oral dose pharmacokinetic profile of yohimbine hydrochloride. In this study, thirty-two healthy volunteers were given yohimbine at doses of, 5.4 mg, 3 times/day; 10.8 mg, 3 times/day; 16.2 mg, 3 times/day, or 21.6 mg 2 times/day, for six days. Plasma catecholamine levels and mood/anxiety-inventory scores

were measured. The pharmacokinetic profile of yohimbine was determined after the first and last dose. Yohimbine exhibited one-compartment elimination in most subjects, with dose-dependent increases in the maximal concentration (C_{max}) and in the AUC. The authors reported no evidence of drug accumulation. At least two subjects in each treatment group exhibited two-compartment elimination of yohimbine, however at day 7 of the study no significant increases of AUC, C_{max}, and terminal elimination half-time were recorded. The reported increase in plasma catecholamine levels was significantly correlated to both the average yohimbine AUC and C_{max}, but there were no significant effects on heart rate, blood pressure, or anxiety/mood-inventory scores. The single- and multiple-dose pharmacokinetic profile of yohimbine exhibits a substantial degree of interindividual and intraindividual variability, possibly resulting from variability in first-pass and hepatic metabolism.

The pharmacokinetics of yohimbine and its two metabolites, 10-hydroxyyohimbine and 11-hydroxyyohimbine, were investigated in 12 healthy male subjects after administration of yohimbine (5 mg, i.v. followed by 8 mg, oral) (Le Corre et al., 1999). Among the subjects treated, one was found to be a slow hydroxylator of yohimbine. The oral bioavailability of yohimbine was found to be low and extremely variable (22.3 ± 21.5 %). The oral absorption was also reported to be low by the authors, possibly due to the formulation used in this study Total plasma clearance of yohimbine following intravenous dosing was 0.728 ± 0.256 ml/min whereas renal clearance was negligible (0.001 +- 0.002 ml/min). Based on the steady-state volume of distribution (Vss), yohimbine had a relatively low distribution (Vss 23.2 ± 12.1 l). The overall renal excretion of yohimbine, 10-hydroxyyohimbine and 11-hydroxyyohimbine, expressed as percent of the dose of yohimbine administered, were not different following intravenous and oral dosing, and were around 0.1, 0.2 and 14 %, respectively. Following intravenous dosing of yohimbine, the mean apparent terminal half-life of 11-hydroxyyohimbine (347 ± 63 min) was almost four times higher than that of yohimbine (91.0 ± 33.6 min), suggesting an elimination rate-limited kinetics for 11-hydroxyyohimbine.

Le Corre et al. (2004) investigated the differences in the metabolism of yohimbine and how these variations influence the sympathetic effects exerted by yohimbine. The study was conducted in 172 individuals (85 men; 87 women) who were administered yohimbine as intravenous infusion (initial bolus: 125 µg/kg bw for three minutes, followed by 1 µg/kg bw/min for 12 minutes). Plasma yohimbine and its metabolite 11-hydroxyyohimbine were measured, showing greater than 1000-fold variability, with 17 individuals showing no metabolism. Non-metabolisers differed from the other subjects included in the study in ethnicity but not in age, sex, body *habitus*, blood pressure, heart rate, or family history of hypertension. Bimodality of metabolism was suggested by frequency histogram, as well as maximum likelihood and cluster analysis. Among ethnic groups, subjects of European ancestry had the highest frequency of non-metabolism. As part of this study, an *in vitro* microsomal oxidation experiment was performed to investigate the possible different activities of the two cytochrome P450 polymorphic variants CYP2D6 and CYP3A4. The results suggested that the major route of metabolism of yohimbine to 11-hydroxyyohimbine was likely to occur via CYP2D6. However, *in vivo*, both CYP2D6 and CYP3A4 were necessary to predict metabolism. Non-metabolisers had greater activation of sympathetic nervous system activity. Yohimbine increased blood pressure, an effect mediated haemodynamically by elevation of cardiac output rather than systemic vascular resistance. Blood pressure and cardiac output responses did not differ between metaboliser and non-metaboliser groups.

In a randomised, double-blind, placebo controlled study, the effects of oral administration of yohimbine on gastrointestinal transit, satiation and plasma catecholamines were investigated. The possible correlation between sympathetic and gastrointestinal effect of yohimbine and the differences in the two cytochrome P450 genotypes, CYP2D6 and CYP3A4, was also studied (Bharucha et al., 2008). In the study, 30 healthy volunteers (15/treatment group; 25 women and 5 men) were randomised to yohimbine 16.2 mg orally three times daily or identical placebo for 7 days. Gastric emptying, small intestinal, and colonic transit by scintigraphy, bowel habits, haemodynamics and plasma catecholamines were evaluated. Genotyping for cytochrome P450 polymorphic variants (CYP2D6 and CYP3A4) was performed in 25 of 30 subjects and the relationship between drug metaboliser status predicted by CYP2D6 and CYP3A4 and effects of yohimbine were assessed.

Compared to placebo, yohimbine increased diastolic blood pressure, plasma noradrenaline concentrations and maximum tolerated volume during the satiation test. However, yohimbine did not affect gastrointestinal transit. Based on CYP2D6 and CYP3A4 alleles, 7 subjects were classified as extensive metabolisers and 18 as poor metabolisers of yohimbine. In the group of poor metabolisers, yohimbine had a greater increase in plasma noradrenaline, lower maximum tolerated volumes and faster colonic transit than in the extensive metabolisers. These data suggest that CYP2D6 and CYP3A4 genotypes which determine the metabolism of yohimbine may influence its sympathetic and gastrointestinal effects.

The pharmacokinetic behaviour of (3,5,6-^{3}H)-raubasine was investigated in five human subjects given an oral administration of 240 µg/kg/bw (Marzo et al., 1977). By the oral route, peak plasma levels of radioactivity appeared in human subjects 1 hour post dosing. In humans, three-day cumulative urinary and faecal excretions of radioactivity accounted respectively for 29 % and 24 % of the dose.

3.1.3. Summary of ADME data

There are no data on ADME of alkaloids after administration of yohimbe preparations such as extracts in both animals and humans.

The major alkaloid yohimbine, when administered alone in humans, is rapidly absorbed and the oral bioavailability shows great variability, ranging from 7 % to 87 % whereas an interindividual variability was also found in the pharmacokinetic parameters of yohimbine. A rapid entry of yohimbine into the brain and a slow rate of elimination from serum and brain were observed in rats receiving an intravenous administration of yohimbine. In liver, the major biotransformation was via CYP2D6 to 11-hydroxy-yohimbine, a metabolite exhibiting similar adrenergic effects than yohimbine. Because of the genetic polymorphism of expression of this cytochrome P450, the genotypes may influence the sympathetic and gastrointestinal effects of yohimbine between individuals. The renal excretion of yohimbine, 10-hydroxyyohimbine and 11-hydroxyyohimbine were around 0.1, 0.2 and 14 %, respectively.

Regarding raubasine, in human subjects given tritiated raubasine orally, the urinary and fecal excretions measured within three days accounted for 29 % and 24 % of the radioactive dose, respectively.

3.2. Toxicological data

3.2.1. Acute toxicity

3.2.1.1. Yohimbe bark and its preparations

No data are available.

3.2.1.2. Yohimbine and other yohimbe alkaloids

Mice

A dose of 20 mg/kg bw of yohimbine injected subcutaneously (s.c.) in albino male mice (T.T. strain; body weight ranging from 18 to 25 g) produced ptosis and slight sedation; the effects lasted for 2 to 4 hours. Higher doses of yohimbine caused prostration and slightly higher sensitivity. About 30 min after s.c. injection, mice exhibit intermittent bouts of clonic convulsions which often continued intermittently for several hours (Quinton, 1963).

Upon i.v. injection, the LD_{50} for yohimbine in mice was 16 mg/kg bw and 65 mg/kg bw after oral exposure (Blaschek et al., 2006).

3.2.2. Short-term and subchronic toxicity

No data for yohimbe bark, its preparations and its alkaloids are available.

3.2.3. Genotoxicity

3.2.3.1. Yohimbe bark and its preparations

No *in vitro* data are available which allow to assess the genotoxicity of yohimbe bark or its preparations.

A significant increase in the frequency of aneuploids and total chromosomal aberrations in germ cells was reported in one study after prolonged (90 days) oral (by gavage) treatment of Swiss albino mice with yohimbe bark powder (Al-Majed et al., 2006). However, the Panel noted some major flaws in the experimental protocol and data presentation in the work of Al-Majed and co-workers. In particular the Panel noted the inclusion of univalents in the computation of chromosomal aberrations in metaphase I spermatocytes which is highly influenced by technical artefacts' and analyses of aneuploids which should have been distinguished between hypo- or hyperhaploid metaphase II spermatocytes. In addition, the increase in dominant lethal mutations as measured by the pre- and post-implantation loss in week 2 after treatment during the entire spermatogenic cycle and not in week 1 after treatment cannot be explained. Therefore the Panel considered that no conclusions can be drawn from this study.

3.2.3.2. Yohimbine and other yohimbe alkaloids

Raubasine was studied using the SOS Chromotest in *E. coli* and the induction of gene conversion, crossing-over and reverse mutation in the yeast diploid strain XS2316. The authors concluded that raubasine is neither genotoxic nor mutagenic nor recombinogenic in microbial systems (von Poser et al., 1990).

No other relevant data on genotoxicity for yohimbine or other alkaloids of yohimbe bark are available.

3.2.4. Chronic toxicity and carcinogenicity

No data for yohimbe bark or its preparations are available. However, in a poorly reported study, raubasine was administered orally in doses of 0, 5, 10, 20 and 40 mg/kg bw/day to rats (strain not specified) for 24 weeks. The authors concluded that, on the basis of measurement of body weight gain, examination of blood parameters and histopathological examinations that there was no indication of a chronic intoxication (Kroneberg, 1958).

3.2.5. Reproductive and developmental toxicity

3.2.5.1. Yohimbe bark and its preparations

In the study by Al-Majed et al. (2006), adult male Swiss albino mice were treated orally (by gavage) for 90 days with 0 (controls: 0.3 ml tap water/mouse), 188, 375 or 750 mg/kg bw/day of an aqueous suspension of yohimbe bark powder (yohimbine content not specified) of *P. yohimbe*. In the first and second week after treatment, 10 males were mated with 30 untreated females. Each of the following parameters were evaluated: reproductive organ weight, motility and sperm count (20 mice); spermatozoa morphology (20 mice); rate of pregnancy and mean implants (total number and number of live and dead implants); cytology of testes chromosomes (20 mice); biochemical estimation of proteins, RNA, DNA, malondialdehyde (MDA), non-protein sulphhydryl (NP-SH) and hormones. The treatment with yohimbe bark powder at 750 mg/kg bw/day caused a significant increase in relative weight of the seminal vesicles, decrease in motility and count of spermatozoa, and an increase in the number of abnormal spermatozoa. Furthermore, an increase in levels of estradiol, prolactin and testosterone was observed. Male fertility was decreased in the first and second week of mating after treatment. The pre- and post- implantation loss was increased in the second week of mating; this finding cannot be explained as animals were treated for more than an entire spermatogenic cycle. The biochemical parameters showed increase of MDA and depletion of NP-SH, proteins, RNA and DNA in the testicular cells in the 375 and 750 mg/kg bw/day groups (Al-Majed, 2006). The Panel noted that although some of these findings might be indicative of an effect on male reproductive function, no definitive conclusions can be drawn from this study due to the inconsistent pattern of results provided by the dominant lethal test, in which post-implantation losses were only decreased in matings in week two.

3.2.5.2. Yohimbine and other alkaloids

No data are available.

3.2.6. Human data

3.2.6.1. Yohimbe bark and its preparations

Case reports

Ruck et al. (1999) reported a case of a 63-year-old man who exhibited a hypertensive crisis with a blood pressure of 240/140 mm Hg, an acute onset of severe headache and weakness. The electrocardiogram showed a sinus tachycardia. The man denied any medical history including hypertension or any prescribed medicine. But he had been taking a yohimbine-containing herbal product for treatment of impotence over the previous month (one tablet per mouth daily, as per the package directions). No further details are given.

3.2.6.2. Yohimbine

Case reports

Price et al. (1984) described three patients who experienced yohimbine-induced manic symptoms. Yohimbine dose was not clearly identified.

In an overview some cases of side effects are mentioned including anxiety and agitation in addition to hypertension (Pittler et al., 2005).

Giampreti et al. (2009) described a 37-year-old bodybuilder who was admitted to the hospital with malaise, vomiting, loss of consciousness, and repeated seizures after ingestion of 5 g of yohimbine. He was comatose, requiring orotracheal intubation. Blood pressure was 259/107 mmHg and heart rate 140 beats/min. The yohimbine blood levels at 3, 6, 14, and 22 hours after ingestion were 5 240; 2 250; 1 530; and 865 ng/ml, respectively, with a mean half-life of 2 hours. The patient recovered without sequelae having been treated to increase the elimination of the substance from the body.

Studies in patients with erectile dysfunction

There are several studies in patients with erectile dysfunction. Doses of 18 mg were used in the studies of Morales et al. (1987) and Riley et al. (1989) and effects have been seen without remarkable non-intended effects. In the study of Reid et al. (1987) also 18 mg were given with a positive outcome in 46 % of the 48 patients participating in the study. The dose was individualised in the study of Susset et al. (1989), 42 mg/day being the highest dose given. Not all of the 82 patients responded (success rate 34 %). In 85 patients who took 30 mg a day (two 5 mg tablets three times daily) for eight weeks, seven percent rated the tolerability fair or poor without giving details on the side effects (Vogt et al., 1997). In a small study (n = 29) drug-related adverse effects occurred in 2 patients in the yohimbine group (7 %) when a dose of 36 mg yohimbine per day was given orally for 25 days (Kunelius et al., 1997). In a study by Teloken et al. (1998) 100 mg yohimbine were given to male patients with erectile dysfunction. The authors report that common side effects were anxiety, increase in cardiac frequency, increased urinary output and headache.

In the clinical studies doses of 18 mg/person/day and 100 mg/person/day were given. The intended effect was seen in patients treated with those doses.

The Panel noted that if clinical effects were seen in patients with erectile dysfunction these would result from pharmacological action of yohimbine.

Studies in patients with panic disorders

In 11 patients with panic disorders, 20 mg yohimbine significantly raised systolic blood pressure ($F = 3.07$, $p < 0.03$), plasma noradrenaline levels ($F = 12.11$, $p < 0.001$) and cortisol levels ($F = 4.82$, $p < 0.02$), but had no effect on adrenaline levels (Gurguis, 1997). Noradrenaline responses were similar in both groups, but patients had higher cortisol responses to yohimbine than controls ($F = 7.14$, $p < 0.01$) dose 20 mg. Anxiety scores were also higher after yohimbine dosing.

Studies in patients with hypertension

Yohimbine (0.2 mg/kg bw, orally) caused a lesser increase in the plasma concentrations of noradrenaline in hypertensive patients (+ 67 %) than in normotensive subjects (+ 178 %) and a pressor response in hypertensive (but not in normotensive) patients (Damase-Michel et al., 1993). These results are consistent with an alteration in the balance of α-adrenoreceptors (for example presynaptic α_2-adrenoreceptor desensitisation and post-synaptic α_1-adrenoreceptor hyper-responsiveness) which would help to develop and/or maintain arterial hypertension.

In the study of Musso et al. (1995), 10 mg yohimbine induced a significant increase in diastolic pressure only in the hypertensive patients and not in the healthy controls. Plasma noradrenaline was increased significantly in both yohimbine-treated groups, but the percent increase of plasma noradrenaline after the standing test was decreased significantly only in the healthy yohimbine-treated subjects. Plasma dopamine was increased significantly only in the healthy yohimbine-treated subjects.

Studies in patients with orthostatic hypotension

In 35 patients with severe orthostatic hypotension due to multiple system atrophy or pure autonomic failure, the effect of placebo, phenylpropanolamine (12.5 mg and 25 mg), yohimbine (5.4 mg), indomethacin (50 mg), ibuprofen (600 mg), caffeine (250 mg), and methylphenidate (5 mg) was determined on seated systolic blood pressure. Significant increases in systolic blood pressure can be seen in the patients with phenylpropanolamine in low doses or yohimbine or indomethacin (Jordan et al., 1998).

Studies in healthy volunteers

In a study by Galitzky et al. (1988) in fasting healthy subjects oral yohimbine administration (0.2 mg/kg bw) produced elevated plasma concentrations of noradrenaline, glycerol and non-esterified fatty acids without significant action on heart rate or blood pressure during the time-course of the experiment. The same group showed that the same reaction was seen in obese and non-obese women with the same dose (oral yohimbine administration, 0.2 mg/kg bw) (Berlan et al., 1991). This dose induced lipid mobilization (increase in plasma non-esterified fatty acids) without significant action on plasma glucose, insulin levels, heart rate or blood pressure during the time-course of the experiment (240 min). Plasma noradrenaline (but not adrenaline) concentrations were increased (100 %) after oral yohimbine administration.

In a study in healthy young volunteers oral yohimbine (20 or 40 mg) causes dose-dependent increases in blood pressure, heart rate, and plasma noradrenaline. The data indicated that yohimbine increases plasma noradrenaline levels by increasing the rate of noradrenaline release from sympathetic nerves, and probably increases adrenaline release from the adrenals (Murburg et al., 1991). The results are in agreement with previous studies.

The effect of the selective α_2-adrenergic receptor antagonist yohimbine on platelet aggregation was evaluated in healthy subjects (Berlin et al., 1991). Yohimbine administered orally selectively antagonised adrenaline but not collagen, arachidonic acid, or adenosine diphosphate-induced *ex vivo* platelet aggregation. The lowest dose of yohimbine that significantly inhibited adrenaline-induced platelet aggregation was 8 mg. The inhibitory effect of yohimbine on platelet aggregation lasted 10 h with the 12 mg dose. At the doses studied (4, 8, and 12 mg), yohimbine did not modify blood pressure, standing heart rate, or plasma catecholamine or glucose concentrations. A dose of 12 mg of yohimbine moderately but significantly accelerated supine heart rate (mean maximal increase, 7 ± 3 beats/min).

The effects of oral administration of the α_2-adrenergic receptor antagonists yohimbine (20 mg) were tested concerning the effects on mood and anxiety states, physiological indexes, plasma cortisol levels, and plasma levels of the noradrenaline metabolite MHPG (Krystal et al., 1992). Yohimbine had a similar profile as the comparator idazoxan which increased plasma MHPG, plasma cortisol, systolic and diastolic blood pressure, and Panic Attack Symptom Scale scores in healthy subjects.

Impulsivity was assessed in healthy volunteers using the Immediate and Delayed Memory Tasks after one or two doses of yohimbine (Swann et al., 2005). Doses of yohimbine were titred according to the blood pressure response and doses up to 40 mg/h were given. Yohimbine was associated with a dose-related increase in impulsive Immediate Memory Tasks commission errors, with an increase of > 50 % relative to baseline at the higher dose as compared to placebo.

3.2.6.3. Raubasine

Studies in patients

Raubasine has been used in a variety of clinical conditions. The clinical studies were performed at times in which detailed description of patients and endpoints was not in use and also the systematic evaluation of the patients concerning possible adverse effects was not part of an evaluation of a new

treatment and therefore the publications are less suited to get information on the effects of raubasine in humans. Nevertheless the studies which have been found in a literature search are reported here.

In explorative studies 18 patients with peripheral arterial disease of various origins have been treated with 3 mg raubasine daily by the oral route (Pieri et al., 1957). Further 9 patients, with tachycardia and hypertension because of Basedow's disease, were also treated with the same dosage. No details on the patients and only same examples of clinical details are given. The authors do not report whether adverse effects have been observed.

Pieri et al. (1958) published a case series of 92 patients in which raubasine was given at daily doses of 3 mg and in some patients of 5 mg by the oral route. The patients suffered from coronary heart disease, hypertension and symptoms of cerebral arterial disease. No adverse effects were noted.

A case series of 13 patients was reported by Robert (1962) in which raubasine (Hydrosarpan®) was used to lower the elevated blood pressure. No dosage schedule is given in the publication and no data are given concerning possible adverse effects.

In a study in 65 patients with peripheral arterial disease (Starace and Noferi, 1963) raubasine was given in daily doses of 4-8 mg intravenously or 8-12 mg orally, divided in 2-3 doses. No side effects were observed besides gastric discomfort even when the treatment lasted up to 40-60 days.

In 22 patients with peripheral arterial disease of the lower extremities and five patients with peripheral arterial disease of the upper extremities the effects of raubasine (3 times 5 mg for 3 weeks orally) was investigated (Perrin, 1965). The author reported that one patient had to withdrawn from the study because of adverse effects which were manifested as burning pain of the stomach.

Pluvinage (1965) carried out a study in 30 patients with different neurological and psychiatric diseases. The patients received 15 to 60 mg of raubasine daily for 3 weeks by the oral route. The author reported on blood pressure changes (decline of 10 to 20 mmHg) which after 10 to 20 days returned to pre-trial values. Other non-therapeutic effects have not been reported. The clinical judgment on the improvement was descriptive without clear endpoints and changes in electroencephalograms were also reported.

In another study, 100 patients with chronic arterial disease were treated with raubasine (Lamuran®), 20 mg orally, three times daily, for three weeks (Koch and Eide, 1972). No adverse effects were reported besides one case of allergic dermal reaction. The authors also reported that they observed a fall in blood pressure in patients in which the drug was given until the day where they underwent anaesthesia because of vascular surgery. No other details were reported.

Studies in healthy volunteers

Healthy volunteers received infusions of 20 mg and 40 mg raubasine of 5 minutes duration. Cardio-vascular parameters were measured (Molzahn and Lohmann, 1973). A dose of 20 mg raubasine elicited only slight effect on cardiac output (8 % increase) whereas immediately after the end of infusion of 40 mg, cardiac output, heart rate and peripheral venous pressure increased and caused a fall of central venous pressure. As a reflex reaction, arterial pressure was increased after 15 and 30 minutes. No subjective side effects were reported in the publication.

The study of Neuman et al. (1986) investigated the effect of raubasine on platelet biological function in 14 patients in an *ex vivo* experiment with adenosine diphosphate (2.5 and 5.0 x 10^{-6} mol/l), collagen (0.05 mg/ml), and adrenaline (1.68 x 10^{-4} mol/l) as inducing agents. The patients received 3 times 20 mg raubasine, orally, daily for six weeks. In 12 out of the 14 patients a reduction in platelet aggregation in at least 2 of the 3 test curves was observed. This reduction was statistically significant for collagen ($p < 0.02$) and adrenaline ($p < 0.01$). A statistically significant ($p < 0.05$) prolongation of the latency period of aggregation produced by collagen was found in 12 out of 14 patients and a

prolongation of recalcification time produced by the reduction in platelet factor 3 was found in 9 out of 14 patients. The patients underwent clinical and standard blood tests. The authors reported that no remarkable results were observed.

Raubasine appears not to show subjective and objective adverse effects in doses less than 10 mg daily (approximately 0.15 mg/kg bw/day) when given orally.

3.2.6.4. Other yohimbe bark alkaloids

No data are available.

3.2.7. Mode of action of yohimbine and raubasine

Yohimbine is an antagonist acting at α_2-adrenoreceptors which enhances noradrenaline release and increases sympathetic activity. α_2-adrenoreceptors are found in the vasculature. Postsynaptic α_2-adrenoreceptors have been identified by Jie et al. (1984). The same group also provided evidence for the existence of presynaptic α_2-adrenoreceptors (Jie et al., 1987). α_2-adrenoreceptors are also found in the central nervous system. Hence, the effects on blood pressure, heart rate and central nervous effects seen after yohimbine administration are explained by its effect on the α_2-adrenoreceptors.

Raubasine is an alkaloid which possesses pre- and postsynaptic α-adrenoreceptor blocking activity. Its postsynaptic blocking properties are more pronounced than that of yohimbine as shown in the rat vase deference model (Demichel et al., 1981). In the pithed rat it preferentially acts at α_1-adrenoreceptors but has also blocking activity at the α_2-adrenoreceptors. Compared to yohimbine which mainly blocks the α_2-adrenoreceptors the activity of raubasine at the α_2-adrenoreceptor is low (Demichel et al., 1982; Roquebert and Demichel, 1984).

4. Discussion

EFSA was asked to assess the safety in use of Yohimbe and its preparations when consumed as component of food, e.g. in food supplements. The risk assessment is carried out according to the EFSA Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009).

Concerns had been raised by an EU Member State Authority regarding a potential risk to consumers linked with the intake of yohimbe bark extracts containing products to treat sexual dysfunction and erectile problems. Consequently, the Commission has initiated the procedure under Article 8 (2) of Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods, for Yohimbe. Therefore EFSA has been asked to review the relevant existing scientific data on the possible link between the intakes of Yohimbe and a harmful effect on health and to provide advice on a tolerable upper intake level (UL) for Yohimbe, for the general population, and as appropriate, for vulnerable subgroups of the population. In the absence of an UL, advice on a daily intake of Yohimbe that does not give rise to concerns about harmful effects to health should be provided.

In addressing the Terms of Reference, the Panel noted that the term "tolerable upper intake level" was used by EFSA so far only for nutrients, such as vitamins or minerals, to describe the maximum level of total chronic daily intake judged to be unlikely to pose a risk of adverse health effects to humans. The Panel considered that the use of this term may not be appropriate for botanicals and botanical preparations being constituents of food supplements or other food products, especially in cases where the botanicals/botanical preparations or their main components have known medical uses based on scientifically established pharmacological properties and/or where the botanicals/botanical

preparations cannot be regarded as a component of the normal diet. Using the term "tolerable upper intake level" for botanicals and botanical preparations could lead to the misinterpretation that they could play a similar role in human nutrition as minerals and vitamins, which differ from them inter alia in being in general constituents of the normal diet and in being in many cases essential.

Food supplements containing yohimbe bark or its preparations are commercially available to improve sexual and athletic performance and for the enhancement of sexual satisfaction. The use of such products is also promoted for weight loss. According to the information provided by the EHIA and the ERNA, in general these products are not marketed in Europe. The Panel however noted that they are offered via internet, often in combination with other substances (e.g. caffeine).

Yohimbe bark consists of dried bark of the trunk and branches of *P. yohimbe*. Toxicologically relevant compounds of yohimbe bark are indole alkaloids. Total alkaloid content data vary, depending on a number of botanical and environmental factors. Also, depending on the analytical method used results of analysis may vary to a high degree. The major alkaloid is yohimbine, accompanied by a number of stereoisomers and other related compounds which are associated with proven or potential biological activity (e.g. raubasine). The reported value of total alkaloid content of the bark varies over a wide range, from about 5 to over 150 mg/g, with a value around 10 mg/g being most often found for yohimbine whereas for the individual stereoisomers of yohimbine the reported values are in the range of 0.3 to 4.6 mg/g. The concentration of raubasine and corynantheine is reported to be around 0.4 mg/g and 0.05 mg/g, respectively.

No specifications for yohimbe bark or its preparations such as extracts for the use in food are known nor is there information on standardisation of the extracts for use in food with regard to the ratio of extracted material to starting material, extraction solvent or content of biologically active ingredients.

There are no official inter-laboratory validated methods for determination of yohimbine and accompanying alkaloids in food, although a single-laboratory validated method for the determination of yohimbine in commercial products has been described.

The actual content of yohimbine versus the declared quantity in the label of food supplements was measured in studies carried out in the US. The results showed that yohimbine levels greatly vary among the different products and that information reported on the label of the existing food supplements do not generally correspond with the quantities analytically determined.

Regarding the specifications, the Panel noted that quantitative data for alkaloids other than yohimbine in yohimbe bark preparations in food supplements are missing but would be needed in view of their known or potential biological activity.

Yohimbine is an antagonist acting at α_2-adrenoreceptors, which enhances noradrenaline release and increases sympathetic activity. Pre- and postsynaptic α_2-adrenoreceptors have been identified and α_2-adrenoreceptors are also found in the central nervous system. Hence, the effects on blood pressure, heart rate and central nervous effects seen after yohimbine administration are explained by its effect on the α_2-adrenoreceptors. Raubasine acts mainly as an antagonist of α_1-adrenoreceptors.

The pharmaceutical use of yohimbe bark and preparations thereof is described in older literature. At present, in the European Union the only existing monograph (Commission E) states that there is insufficient proof of efficacy and the unforeseeable correlation between risk and benefit. According to information made available by the EMA, no assessment report on safety and efficacy is available or currently expected from the HMPC since yohimbe bark is not on the HMPC priority list. It is important to note that this lack of priority is a consequence of the known risks associated with the use of yohimbe bark and its preparations as herbal medicinal product.

For the main alkaloid yohimbine, authorised medicinal products exist, containing yohimbine hydrochloride as active ingredient. It is given orally in the treatment of erectile dysfunction in doses of

5–10 mg, 2–3 times daily, the typical treatment period being 8 weeks. Concerning contraindications and warnings the following conditions are mentioned: hypersensitivity to the active ingredient, cardiac disorders (especially heart disease, tachycardic arrhythmia), hypertension, hypotension, greatly impaired kidney or liver function, ulcer (stomach or intestine), glaucoma, psychiatric disorders, particularly mood disorders and anxiety as well as concomitant use of central nervous acting drugs. Because no adequate clinical experiences with treatment in women exist it is also not possible to determine effects on a fetus during pregnancy. Adverse effects listed in the summary of product characteristics are: headache, nausea, increased urinary urge; insomnia, anxiety, restlessness, irritability (common); increase of blood pressure and pulse rate, palpitation, dizziness, vomiting, anorexia, gastric complaints, diarrhoea, flush, sweating, shivering, allergic reactions, nervousness (uncommon); hypotension, tremor, bronchospasm, dysuria, decreased urge, genital pains, exanthema (very rare).

The alkaloid raubasine given orally is used as an adjuvant in the treatment of peripheral arterial disorders. The dose is 10–20 mg, 2–3 times daily. Contraindications and warnings include hypersensitivity to the active substance, serious heart disease, haemorrhagic syndrome or intracranial hypertension, uncompensated heart failure, valvular stenosis, significant reduction of the pulmonary circulatory bed, glaucoma, the first three months of pregnancy and the usage during or within two weeks after treatment with monoaminooxidase inhibitors. Adverse effects listed in the summary of product characteristics are: dizziness, hypotension, sweating, flushing (rare), appearance of confusion, tachycardia, nausea, allergic reactions (occasionally). In the case of heart disease or other general disorders discontinuation of therapy may be required.

As for national regulations the use of yohimbe bark and its preparations is specifically prohibited in foods and food supplements, in several European countries (e.g. United Kingdom, Netherlands, Belgium, Denmark, Czech Republic), as well as in Canada, Australia and New Zealand.

It was not possible to assess exposure to yohimbe bark and its preparations due to lack of data. An exposure assessment to yohimbine from food supplements containing yohimbe bark was performed using data available from the literature. Quantitative data for alkaloids other than yohimbine in yohimbe bark containing food supplements are missing and, therefore, no exposure assessment could be performed for them. These data would be specially needed for substances with known pharmacological activity, e.g. raubasine.

The maximum dose of yohimbine estimated from a single serving of food supplement (18.8 mg, see Table 3) was higher than the highest single dose of authorised medicinal products (10 mg, see Table 4). Maximum daily exposure to yohimbine from food supplements has been estimated to be up to 75 mg/person, which is higher than the maximum approved daily dose of yohimbine from use as a medicinal product (up to 30 mg/person, see Table 4).

In general botanicals such as yohimbe bark and botanical preparations such as yohimbe bark extracts for use in food supplements should be evaluated based on existing data on the chemical specifications and existing toxicological data, including read across where appropriate, for the individual botanical/botanical preparation. Therefore, the Panel gave priority to the toxicological studies investigating yohimbe bark and its preparations and then on yohimbine as the main alkaloid in yohimbe bark and the only alkaloid for which occurrence had been shown and quantified in food supplements containing yohimbe bark.

There are no available data describing the ADME of yohimbe alkaloids after administration of yohimbe bark preparations, such as extracts. In an *in vitro* study, the alkaloids of yohimbe bark extract, yohimbine, raubasine, and corynanthine have been described to be transported across human Caco-2 cells monolayers (Ma and Yang, 2008). When administered alone in humans, the major alkaloid yohimbine is rapidly absorbed and the oral bioavailability ranged from 7 % to 87 % (Guthrie et al., 1990). The great variability of absorption of yohimbine in humans would be due to both interindividual and dietary factors. In terms of distribution, a rapid entry of yohimbine into the brain

and a slow rate of elimination from serum and brain were observed in rats receiving an intravenous administration of yohimbine (Hubbard et al., 1988). In humans, there is a significant correlation between plasma noradrenaline levels and yohimbine AUC or C_{max} (Sturgil et al., 1997). In liver, the major biotransformation was oxidation to 11-hydroxyyohimbine, a metabolite exhibiting similar adrenergic effects as yohimbine. This route of metabolism was found to depend on the cytochrome P450 polymorphic variants CYP2D6 and CYP3A4, causing interindividual differences in sympathetic and gastrointestinal effects of this alkaloid, as clinically observed in humans. In humans, the renal excretion of yohimbine, 10-hydroxyyohimbine and 11-hydroxyyohimbine were around 0.1, 0.2 and 14 %, respectively. There are only a few data on disposition of raubasine. In human subjects given tritiated raubasine orally, the urinary and fecal excretions of radioactivity measured for three days accounted respectively for 29 % and 24 % of the dose (Marzo et al., 1977).

No short-term or (sub)chronic toxicity and carcinogenicity studies on yohimbe bark or its preparations were available.

In a limitedly reported study, raubasine was administered by gavage to rats at doses of 0, 5, 10, 20 and 40 mg/kg bw/day for 24 weeks. No effects on body weight, haematology and histopathology were observed (Kroneberg, 1957).

No *in vitro* data on genotoxicity studies of yohimbe bark, its preparations or of yohimbine are available. The Panel noted the results of a genotoxicity assay in germ cells of male mice which was performed after 90 days of treatment with an aqueous suspension of yohimbe bark powder (yohimbine content not specified). However, major flaws in the experimental protocol and in the presentation of the data prevented the Panel from considering this study for risk assessment.

In the same study, a number of parameters of male fertility were also measured, however the Panel had reservations about this study and considered that no conclusions could be drawn concerning the reproductive toxicity of yohimbe bark.

Raubasine was negative in the SOS Chromotest in *E. coli* and did not induce gene conversion, crossing-over or reverse mutations in the yeast diploid strain XS2316 (von Poser et al., 1990).

Regarding human data on the use of yohimbe bark extract, only one case report has been found in the literature. Ruck et al. (1999) reported a case of a 63-year-old man who exhibited a hypertensive crisis following administration of a yohimbine-containing herbal product.

No clinical studies investigating effects of yohimbe bark or its preparations are available, thus the Panel considered the following evidence coming from studies on yohimbine and raubasine. No human data were found for other yohimbe bark alkaloids.

Human data encompass several case reports with yohimbine intoxications for which severe symptoms (hypertensive crisis, manic symptoms, anxiety, agitation, loss of consciousness) have been described (Price et al., 1984; Pittler et al., 2005; Giampreti et al., 2009). Clinical studies have been performed in a whole array of indications such as erectile dysfunction (Morales et al., 1987; Riley et al., 1989; Susset et al., 1989; Kunelius et al., 1997; Vogt et al., 1997; Teloken et al.,1998), panic disorders (Gurguis, 1997), hypertension (Damase-Michel et al., 1993; Musso et al., 1995) and orthostatic hypotension (Jordan et al., 1998). Doses between 5.4 mg and 100 mg daily were used whereby doses up to 18 mg daily elicited no subjective side effects but doses as low as 5.4 mg resulted in significant increases in systolic blood pressure (Jordan et al., 1998). Several studies in healthy volunteers have been carried out investigating various endpoints. Plasma concentrations of noradrenaline, glycerol and non-esterified fatty acids were increased (Galitzky et al., 1988; Berlan et al., 1991) as was also blood pressure and heart rate (Murburg et al., 1991). Furthermore, antagonising of adrenaline-induced platelet aggregation was shown (Berlan et al. 1991). Mood, anxiety states, physiological indexes, plasma cortisol levels, and plasma levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol was influenced by 20 - 40 mg yohimbine (Krystal et al., 1992).

Yohimbine was associated with a dose-related increase in impulsive omission errors (Swann et al., 2005). In these studies in healthy volunteers 8 mg was active to antagonise platelet aggregation without modifying blood pressure, standing heart rate, or plasma catecholamine or glucose concentrations. Twelve milligrams of yohimbine moderately but significantly accelerated supine heart rate (mean maximal increase, 7 ± 3 beats/min).

The effects which were observed with the single alkaloid yohimbine may also be observed after yohimbe bark intake. However, there are no data allowing an extrapolation of the dose-response relationship observed after yohimbine to the mixture of substances contained in yohimbe bark. This limits the use of the human data of yohimbine in the risk assessment of yohimbe bark.

In the human studies evaluated in the present opinion, raubasine did not show adverse effects in oral doses less than 10 mg/person/day (corresponding to approximately 0.15 mg/kg bw/day).

Overall the Panel noted the following:

- Yohimbe bark preparations are available worldwide as food supplements via internet retailing.
- In West Africa, yohimbe bark preparations were traditionally used e.g. as a general tonic, as a performance enhancer for athletes and as an aphrodisiac.
- In general, botanicals such as yohimbe bark and botanical preparations such as yohimbe bark extracts for use in food supplements should be evaluated based on existing data on the chemical specifications and existing toxicological data, including read across where appropriate, for the individual botanical/botanical preparation.
- Quantitative data for alkaloids other than yohimbine in yohimbe bark preparations in food supplements are not available but are required in view of their known or potential biological activity.
- No specifications for yohimbe bark or its preparations such as extracts used in food supplements are known. There is no information on standardisation of the extracts for use in food supplements with regard to the ratio of extracted material to starting material, extraction solvent or content of biologically active ingredients.
- There are no official inter-laboratory validated methods for determination of yohimbine and accompanying alkaloids in food supplements, although a single-laboratory validated method for the determination of yohimbine in commercial products has been described.
- In several European countries, the use of yohimbe bark and its preparations is specifically prohibited in foods and food supplements.
- According to information made available by the European Medicines Agency, no assessment report on safety and efficacy is available or currently expected from the Committee on Herbal Medicinal Products (HMPC) since yohimbe bark is not on the HMPC priority list. It is important to note that this lack of priority is a consequence of the known risks associated with the use of yohimbe bark and its preparations as herbal medicinal product.
- According to information made available by the EMA, no single ingredient (traditional) herbal medicinal products containing yohimbe bark or its preparations appear to be authorised or registered within the EU.
- For the main alkaloid yohimbine medicinal usage exists in the form of its hydrochloride. It is given orally in the treatment of erectile dysfunction in doses of 5–10 mg, 2–3 times daily, for a typical treatment period of 8 weeks. The alkaloid raubasine is given orally as adjuvant in the treatment of peripheral arterial disorders in doses of 10–20 mg, 2–3 times daily.
- Maximum daily exposure to yohimbine from food supplements has been estimated by the Panel to be up to 75 mg/person, which is higher than the approved daily dose of yohimbine from use as a medicinal product (up to 30 mg/person).
- Based on structural considerations co-exposure to yohimbine and other yohimbe bark alkaloids may be interacting.
- No data are available describing the ADME of Yohimbe alkaloids after administration of yohimbe bark preparations such as extracts.

- When administered alone in humans, the major alkaloid yohimbine is rapidly absorbed and the oral bioavailability ranged very widely from 7 % to 87 %.
- In humans, the major hepatic oxidation of yohimbine to its pharmacologically active 11-hydroxy metabolite is depending on two cytochrome P450 polymorphic variants CYP2D6 and CYP3A4. The differences in metabolite production result in clinically observed interindividual variability in sympathetic and gastrointestinal effects of this alkaloid.
- No experimental data on subchronic or chronic toxicity and carcinogenicity of yohimbe bark, its preparations or of yohimbine are available.
- No *in vitro* data on genotoxicity studies of yohimbe bark, its preparations or of yohimbine are available.
- An *in vivo* genotoxicity assay in germ cells of male mice was performed after 90 days of treatment with yohimbe bark showed some major flaws in experimental protocol and data presentation and no conclusions could be drawn from this study.
- The Panel considered that this study could not be used for the assessment of male fertility and that no adequate experimental data on reproductive and developmental toxicity of yohimbe bark, its preparations or of yohimbine are available.
- No clinical studies investigating effects of yohimbe bark or its preparations are available, thus evidence coming from studies on yohimbine and raubasine was considered. No human data were found for other yohimbe bark alkaloids.
- Available data of a case report on a hypertensive crisis after intake of a yohimbine-containing herbal product for treatment of impotence over the past month are indicative of possible severe side effects of yohimbine. However, based on the information provided in this single case report, it is not possible to ascertain the frequency of occurrence.
- Adverse effects listed in the summary of product characteristics for medicinal products containing yohimbine are: headache, nausea, increased urinary urge; insomnia, anxiety, restlessness, irritability (common); increase of blood pressure and pulse rate, palpitation, dizziness, vomiting, anorexia, gastric complaints, diarrhoea, flush, sweating, shivering, allergic reactions, nervousness (uncommon); hypotension, tremor, bronchospasm, dysuria, decreased urge, genital pains, exanthema (very rare).
- Several of these effects have also been shown in clinical studies of yohimbine. In a study in healthy young volunteers oral yohimbine (20 or 40 mg) caused dose-dependent increases in blood pressure, heart rate, and plasma noradrenaline concentration.
- According to a study in healthy human volunteers, a single oral dose of 4 mg yohimbine /person did not show effects on platelet aggregation and cardiovascular parameters as well as plasma catecholamines and glucose concentrations.

CONCLUSIONS

The present opinion deals with the safety of the bark from *Pausinystalia yohimbe* (K. Schum.) Pierre ex Beille and preparations made from it when used in food, e.g. in the form of food supplements.

Overall the missing information include quantitative data on the composition and specifications of yohimbe bark and its preparations used in food and food supplements covering other alkaloids besides yohimbine, data on the bioavailability of active ingredients from the yohimbe bark extract and data on the toxicity of well specified individual preparations of yohimbe bark and the major yohimbe bark alkaloids, especially regarding subchronic toxicity, genotoxicity and reproductive toxicity.

The Panel concluded that according to the Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA SC, 2009) yohimbe bark and its preparations belong to the category of botanicals/botanical preparations for which the available data are not sufficient to conclude on their safety or to establish a health based guidance value (safety assessment based on available knowledge (Level A) revealed need for further data).

The Panel concluded that based on the information on the use of yohimbe bark and its preparations in food supplements, estimated exposure to yohimbine could be similar to or higher than that at which effects were reported from the use of yohimbine in medicinal products.

REFERENCES

ACS (American Cancer Society), 2008, online. Herbs, Vitamins and Minerals, Yohimbe. Available from http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/herbsvitaminsandminerals/yohimbe?sitearea=ETO

Al-Majed AA, Al-Yahya AA, Al-Bekairi AM, Al-Shabanah OA and Qureshi S, 2006. Reproductive, cytological and biochemical toxicity of Yohimbe in male Swiss albino mice. Asian Journal of Andrology, 8, 469-476.

Arends FGG and Zörnig H, 1938. Hagers Handbuch der Pharmazeutischen Praxis (2nd edition). Verlag von Julius Springer, Berlin, Germany.

Berlan M, Galitzky J, Riviere D, Foureau M, Tran MA, Flores R, Louvet JP, Houin G and Lafontan M, 1991. Plasma catecholamine levels and lipid mobilization induced by yohimbine in obese and nonobese women. International journal of obesity. 15, 305-315.

Berlan M, Le Verge R, Galitzky J and Le Corre P, 1993. Alpha 2-adrenoceptor antagonist potencies of two hydroxylated metabolites of yohimbine. British Journal of Pharmacology, 108, 927-932.

Berlin I, Crespo-Laumonnier B, Cournot A, Landault C, Aubin F, Legrand JC and Puech AJ, 1991 The α_2-adrenergic receptor antagonist yohimbine inhibits epinephrine-induced platelet aggregation in healthy subjects. Clinical Pharmacology andTherapeutics, 49, 362-369.

Betz JM, White KD and der Marderosian AH, 1995. Gas chromatographic determination of yohimbine in commercial yohimbe products. Journal of AOAC International, 78, 1189-1194.

BfR (Bundesinstitut für Risikobewertung), 2012. Risikobewertung von Pflanzen und pflanzlichen Zubereitungen, Pausinystalia yohimbe L. (Yohimbe), Bundesinstitut für Risikobewertung, Wissenschaft 01/2012, 153-165, ISBN 3-938163-76-3, ISSN 1614-3795 (Print), 1614-3841 (Internet), Berlin, Germany.

Bharucha AE, Skaar T, Andrews CN, Camilleri M, Philips S, Seide B, Burton D, Baxter K and Zinsmeister AR, 2008. Relationship of cytochrome P450 pharmacogenetics to the effects of yohimbine on gastrointestinal transit and catecholamines in healthy subjects. Neurogastroenterology and motility, 20, 891-899.

Blaschek W, Ebel S, Hackenthal E, Holzgrabe U, Keller K, Reichling J and Schulz V, 2006. HagerROM 2006: Hagers Handbuch der Drogen und Arzneistoffe (version 5.0). Springer Medizin Verlag, Heidelberg, Germany. CD-ROM

Blumenthal M, Busse WR, Bundesinstitut fur Arzneimittel und Medizinprodukte, 1998. The complete German Commission E monographs, Therapeutic guide to herbal medicines. American Botanical Council, Austin, Texas, USA. xxii, 685 pp.

Brandt W. 1922. Monographie der gattungen *Corynanthe* Wetwitsch und *Pausinystalia* Pierre, Rubieceae (Über die Stammpflanze der Yohimberinde und ihre Verwandten). Archiv der Pharmazie, 260: 49-94.

Chamala RR, 2010. Studies toward the total synthesis of (±)-α-yohimbine by double annulations. Doctoral Dissertation, University of Kentucky, Lexington, KY, USA. 287 pp.

Chen Q, Li P, Zhang Z, Li K, Liu J and Li Q, 2008. Analysis of yohimbine alkaloid from Pausinystalia yohimbe by non-aqueous capillary electrophoresis and gas chromatography-mass spectrometry. Journal of Separation Science, 31, 2211-2218.

Clark LE and Sunderland TCH, 2004. The Key Non-Timber Forest Products of Central Africa: State of the Knowledge. SD Publication Series Office of Sustainable Development Bureau for Africa U.S. Agency for International Development; Technical Paper No. 122, 121-140.

Damase-Michel C, Tran MA, Llau ME, Chollet F, Senard JM, Guiraud-Chaumeil B, Montastruc JL, and Montastruc P, 1993. The effect of yohimbine on sympathetic responsiveness in essential hypertension. European Journal of Clinical Pharmacology, 44, 199-201.

Demichel P, Gomond P and Roquebert J, 1981. Pre- and postsynaptic alpha-adrenoceptor blocking activity of raubasine in the rat vas deferens. British Journal of Pharmacology, 74, 739-745.

Demichel P, Gomond P and Roquebert J, 1982. alpha-Adrenoceptor blocking properties of raubasine in pithed rats. British Journal of Pharmacology, 77, 449-454.

DTU (Danish Technical University) Fødevareinstituttet, online http://www.food.dtu.dk/upload/fødevareinstituttet/food.dtu.dk/projekter/drogelisten/rapport.pdf

Duke JA. 1992. Handbook of phytochemical constituents of GRAS herbs and other economic plants. Boca Raton, FL. CRC Press.

EB6, 1953. Ergänzungsbuch zum Deutschen Arzneibuch (Supplement to the 6th German Pharmacopoeia). Deutscher Apotheker Verlag Stuttgart

EC (European Commission), online. EU Register on nutrition and health claims. Available from http://ec.europa.eu/nuhclaims/?event=register.home

EFSA (European Food Safety Authority), 2012. Compendium of Botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements, EFSA Journal, 10(5):2663. 60 pp.

EFSA SC (EFSA Scientific Committee), 2009. Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. EFSA Journal, 7(9):1249. 19 pp.

EFSA SC (EFSA Scientific Committee), 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal, 10(3):2579. 32 pp.

EMA (European Medicines Agency), 2005. Committee on Herbal Medicinal Products. Public Statement on "CPMP List of Herbal Drugs with serious risks, dated 1992. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089951.pdf

European Pharmacopoeia 7.0, 2011.

Expanded Commission E, online. Herbal Medicine. Yohimbe bark. American Botanical Council, available from http://cms.herbalgram.org/expandedE/Yohimbebark.html

Galitzky J, Taouis M, Berlan M, Riviere D, Garrigues M and Lafontan M, 1988. α_2-Antagonist compounds and lipid mobilization: evidence for a lipid-mobilizing effect of oral yohimbine in healthy male volunteers. European Journal of Clinical Investigation, 18, 587-594.

Giampreti A, Lonati D, Locatelli C, Rocchi L and Campailla MT, 2009.Acute neurotoxicity after yohimbine ingestion by a body builder. Clinical Toxicology, 47,827-829.

Grasing K, Sturgill MG, Rosen RC, Trout JR, Thomas TJ, Kulkarni GD, Maines P and Seibold JR, 1996. Effects of yohimbine on autonomic measures are determined by individual values for area under the concentration-time curve. Journal of Clinical Pharmacology, 36, 814-822.

Gruenwald J, Brendler T, Jaenicke C (editors) 2007. PDR for Herbal Medicines (4th edition). Thomson Healthcare Inc., Montvale NJ, USA.

Gurguis GNM, Vitton BJ and Uhde TW, 1997. Behavioral, sympathetic and adrenocortical responses to yohimbine in panic disorder patients and normal controls. Psychiatry Research, 71, 27-39.

Guthrie SK, Hariharan M and Grunhaus LJ, 1990. Yohimbine bioavailability in humans. European Journal of Clinical Pharmacology, 39, 409-411.

Hajonides van der Meulen T and van der Kerk GJM, 1964. Alkaloids in Pausinystalia Yohimbe (K. Schum.) Ex Pierre. Part I. The paper-chromatographic identification of alkaloids occurring in some yohimbine-containing barks. Recueil des Travaux Chimiques des Pays-Bas, 83,141–147.

Health Canada, 1995, online. Drugs Directorate Policy on Herbals used as Non-medicinal Ingredients in Nonprescription Drugs in Human Use. Available from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/pol/herbnonmed_pol-eng.pdf

Health Canada, 2012a, online. Listing of Drugs Currently Regulated as New Drugs (The New Drugs List). Available from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/newdrug-drognouv/ndrugs_ndrogu-eng.pdf

Health Canada, 2012b, online. Draft Prescription Drugs List. Available from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/drug-medic/pdl_list_ord-eng.pdf

Hedner T, Edgar B, Edvinsson L, Hedner J, Persson B and Pettersson A, 1992. Yohimbine pharmacokinetics and interaction with the sympathetic nervous system in normal volunteers. European Journal of Clinical Pharmacology, 43, 651-656.

Ho AK, Hoffman DB, Gershon S and Loh HH, 1971. Distribution and metabolism of tritiated yohimbine in mice. Archives internationales de pharmacodynamie et de therapie, 194, 304-315.

Hubbard JW, Pfister SL, Biediger AM, Herzig TC and Keeton TK, 1988. The pharmacokinetic properties of yohimbine in the conscious rat. Naunyn-Schmiedeberg's archives of pharmacology, 337, 583-587.

Jie K, van Brummelen P, Vermey P, Timmermans PB and van Zwieten PA, 1984. Effects of exogenous adrenaline and noradrenaline on vascular postsynaptic alpha 1- and alpha 2-adrenoceptors in man. Journal of Hypertension. Supplement, 2, S119-S121.

Jie K, van Brummelen P, Vermey P, Timmermans PB and van Zwieten PA, 1987. Modulation of noradrenaline release by peripheral presynaptic alpha 2-adrenoceptors in humans. Journal of Cardiovascular Pharmacology, 9, 407-413.

Jordan J, Shannon JR, Biaggioni L, Norman R, Black BK and Robertson D, 1998. Contrasting actions of pressor agents in severe autonomic failure. The American Journal of Medicine, 105, 116-124.

Koch G and Eide M, 1972. [Effect of raubasine in treatment of peripheral arterious circulation disorders]. Medizinische Klinik, 67, 1519-1521. [Article in German]

Krystal JH, McDougle C, Woods SW, Price LH, Heninger GR and Charney DS, 1992. Dose-response relationship for oral idazoxan effects in healthy human subjects: comparison with oral yohimbine. Psychopharmacology, 108, 313-319.

Kroneberg, 1958. Pharmacology of the Rauwolfia alkaloid raubasin (gamma-yohimbine, ajmalicine). Naunyn-Schmiedebergs Archiv fur experimentelle Pathologie und Pharmakologie, 233, 72-97. [Article in German.]

Kuhlmann H, 1999. Yohimbin. Potenzkraft von Äquator. Pharmazeutische Zeitung, 47: 11-16.

Kunelius P, Hakkinen and Lukkarinen O, 1997. Is high-dose yohimbine hydrochloride effective in the treatment of mixed-type impotence? A prospective, randomised, controlled double-blind crossover study. Urology, 49, 441-444.

Le Corre P, Dollo G, Chevanne F and Le Verge R, 1999. Biopharmaceutics and metabolism of yohimbine in humans. European journal of pharmaceutical sciences, 9, 79-84.

Le Corre P, Parmer RJ, Kailasam MT, Kennedy BP, Skaar TP, Ho H, Leverge R, Smith DW, Ziegler MG, Insel PA, Schork NJ, Flockhart DA and O'Connor DT, 2004. Human sympathetic activation by alpha2-adrenergic blockade with yohimbine: Bimodal, epistatic influence of cytochrome P450-mediated drug metabolism. Clinical pharmacology and therapeutics, 76, 139-153.

Le Hir A, Goutarel R and Janot M-M, 1953. Extraction et separation de la yohimbine et de ses stereoisomers. Annales Pharmaceutiques Françaises, 11, 546-564.

Le Verge R, Le Corre P, Chevanne F, Doe De Maindreville M, Royer D and Levy J, 1992. Determination of yohimbine and its two hydroxylated metabolites in humans by high-performance liquid chromatography and mass spectral analysis. Journal of Chromatography, 574, 283-292.

Loewy A, 1900. Beiträge zur Wirkung des Yohimbin (Spiegel). Berliner klinische Wochenschrift, 42, 928-930.

Ma L and Yang XW, 2008. Studies on predict of absorption of corynanthine, yohimbine, ajmalicine and ajmaline across human intestinal epithelial by using human Caco-2 cells monolayers. Zhongguo Zhong Yao Za Zhi, 33, 2373-2377. [Article in Chinese]

Madaus G, 1976. Lehrbuch der biologischen Heilmittel. Hildesheim; Georg Olms Verlag (reprint of Madaus G. (1938) Lehrbuch der biologischen Heilmittel. Leipzig; Georg Thieme Verlag)

Marzo A, Ghirardi P, Alessio R and Villa A, 1977. Absorption and excretion of 3H-raubasine in human subjects and dogs. Arzneimittel-Forschung, 27, 2343-2344.

Martindale, 2011. The Complete Drug Reference, 37th edition. Pharmaceutical Press London Chicago

Meulen and Kerk, 1962

Molzahn M and Lohmann FW, 1973. [Circulatory effect of raubasin]. Zeitschrift fuer Kardiologie, 62, 340-352. [Article in German].

Morales A, Condra M, Owen JA, Surridge DH, Fenemore J and Harris C, 1987. Is yohimbine effective in the treatment of organic impotence? Results of a controlled trial. The Journal of Urology, 137, 1168-1172.

Murburg MM, Villacres EC, Ko GN and Veith RC, 1991. Effects of yohimbine on human sympathetic nervous system function. Journal of Clinical Endocrinology and Metabolism, 73, 861-865.

Musso NR, Vergassola C, Pende A and Lotti G, 1995. Yohimbine effects on blood pressure and plasma catecholamines in human hypertension. American journal of hypertension, 8, 565-571.

NTP (National Toxicology Program), 1999. Summary of data for chemical selection: Yohimbe bark extract / yohimbine. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Yohimbe_508.pdf

Neuman J, de Engel AM and Neuman MP, 1986. Pilot study of the effect of raubasine on platelet biological activity. Arzneimittel-Forschung, 36, 1394-1398.

Owen JA, Nakatsu SL, Fenemore J, Condra M, Surridge DH, Morales A, 1987. The pharmacokinetics of yohimbine in man. European journal of clinical pharmacology, 32, 577-582.

Perrin M, 1965. [Raubasine in Arterial Pathology of the Extremities]. Gazette Medicale de France, 72, 1504-1508. [Article in French].

Pieri J, Wahl, M, Casalonga J, Ambrosi G and Doucet R, 1957. [Results from the study of a new sympatholytic alkaloid, raubasine, in therapy of arteritis]. La Presse Medicale, 65, 1569-1571. [Article in French].

Pieri J, Wahl, M and Casalonga J, 1958.[Application of raubasine in the treatment of angina pectoris and cerebral atherosclerosis]. La Presse Medicale, 66, 1523-1525. [Article in French]

Pittler MH, Schmidt K and Ernst E, 2005. Adverse events of herbal food supplements for body weight reduction: systematic review Obesity Reviews, 6, 93-111.

Pluvinage R, 1965. [Experimentation with raubasine in high doses in neurology and geriatrics]. Gazette Medicale de France, 72, 3971-3978. [Article in French]

Price LH, Charney DS. and Heninger GR, 1984. Three cases of manic symptoms following yohimbine administration. American Journal of Psychiatry, 141, 1267-1268.

Quinton RM, 1963. The Increase in the Toxicity of Yohimbine Induced by Imipramine and Other Drugs in Mice. British Journal of Pharmacology and Chemotherapy, 21, 51-66.

Raman V, Avula B, Galal AM, Wang YH and Khan IA, 2013. Microscopic and UPLC-UV-MS analyses of authentic and commercial yohimbe (Pausinystalia johimbe) bark samples. Journal of Natural Medicines, 67:42-50.

Reid K, Surridge DH, Morales A, Condra M, Harris C, Owen J and Fenemore J, 1987. Double-blind trial of yohimbine in treatment of psychogenic impotence. Lancet, 2, 421-423.

Riley AJ, Goodman R, Kellett JM and Orr R, 1989. Double-blind trial of yohimbine hydrochloride in the treatment of erection inadequacy. Sex and Marital Therapy, 4, 17.

Robert P, 1962.[Clinical experience with Raubasine]. Cahiers R. M. F.: bulletin medical-guide du praticien-revue medicale francaise, 76, 557-559. [Article in French]

Roquebert J and Demichel P, 1984. Inhibition of the alpha 1 and alpha 2-adrenoceptor-mediated pressor response in pithed rats by raubasine, tetrahydroalstonine and akuammigine. European Journal of Pharmacology, 106, 203-205.

Ruck B, Shih RD and Marcus SM, 1999. Hypertensive crisis from herbal treatment of impotence. The American Journal of Emergency Medicine, 17, 317-318..

SciFinder, online.

Starace G, Noferi A (1963) [Raubasine in the Medical Treatment of Peripheral Arterial Diseases]. Gazzetta Medica Italiana, 122, 173-175. [Article in Italian]

Sturgill MG, Grasing KW, Rosen RC, Thomas TJ, Kulkarni GD, Trout JR, Maines M and Seibold JR, 1997. Yohimbine elimination in normal volunteers is characterized by both one- and two-compartment behavior. Journal of cardiovascular pharmacology, 29, 697-703.

Sun J and Chen P, 2012. Chromatographic fingerprint analysis of yohimbe bark and related dietary supplements using UHPLC/UV/MS. Journal of Pharmaceutical and Biomedical Analysis, 5, 142-149.

Sunderland TCH, Ngo-Mpeck ML, Tchoundjeu Z, 1999. The ecology and sustainability of Pausinystalia johimbe: an over-exploited medicinal plant of the forests of Central Africa. Outcome of the International Expert Meeting on Non-Wood Forest Products in Central Africa, Cameroon, 10-15 May 1998. 67-77.

Susset JG, Tessier CD, Wincze J, Bansal S, Malhotra C and Schwacha MG, 1989. Effect of yohimbine hydrochloride on erectile impotence: a double blind study. The Journal of Urology, 141, 1360-1363.

Swann AC, Birnbaum D, Jagar AA, Dougherty DM and Moeller FG, 2005. Acute yohimbine increases laboratory-measured impulsivity in normal subjects. Biological Psychiatry, 57, 1209-1211.

Tam SW, Worcel M and Wyllie M, 2001. Yohimbine: a clinical review. Pharmacology & Therapeutics, 91, 215-243.

Tanaka T and Starke K, 1980. Antagonist/agonist-preferring alpha-adrenoceptors or alpha 1/alpha 2-adrenoceptors? European journal of pharmacology, 63, 191-194.

Teloken C, Rhoden EL, Sogari P, Dambros M, Souto C and Ary V, 1998. Therapeutic effects of high-dose yohimbine hydrochloride on organic erectile dysfunction. The Journal of Urology, 159, 122-124.

Timmermans PB, Schoop AM, Kwa HY, Van Zwieten PA, 1981. Characterization of alpha-adrenoceptors participating in the central hypotensive and sedative effects of clonidine using yohimbine, rauwolscine and corynanthine. European Journal of Pharmacology, 70, 7-15.

USDA ARS (United States Department of Agriculture, Agricultural Research Service), online National Genetic Resources Program. *Germplasm Resources Information Network (GRIN)*. National Germplasm Resources Laboratory, Beltsville, Maryland. Available from http://www.ars-grin.gov/cgi-bin/npgs/html/tax_search.pl

Vogt HJ, Brandl P, Kockott G, Schmitz J R, Wiegand M H, Schadrack J and Gierend M, 1997. Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction. International journal of impotence research, 9, 155-161.

von Poser G, Andrade HH, da Silva KV, Henriques AT and Henriques JÁ, 1990. Genotoxic, mutagenic and recombinogenic effects of rauwolfia alkaloids. Mutation Research, 232, 37-43.

Wink M, van Wyk B-E, Wink C, 2008. Handbuch der giftigen und psychoaktiven Pflanzen. Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany, 464 pp.

Zanolari B, Ndjoko K, Ioset JR, Marston A, Hostettmann K, 2003. Qualitative and quantitative determination of yohimbine in authentic yohimbe bark and in commercial aphrodisiacs by HPLC-UV-API/ MS methods. Phytochemical Analysis, 14, 193-201.

ABBREVIATIONS

ANS Panel:	Panel on Food Additives and Nutrient Sources Added to Food
APCI:	atmospheric pressure chemical ionisation
AUC:	area under the concentration-time curve
BfR:	German Federal Institute for Risk Assessment
C_{max}:	maximal concentration
EEA:	European Economic Area
EFSA:	European Food Safety Authority
EHIA:	European Herbal Infusions Association
EMA:	European Medicines Agency
ERNA:	European Responsible Nutrition Alliance
ESI:	electrospray ionisation
ESI:	electrospray ionisation
EU:	European Union
GC:	gas chromatography
HMPC:	Committee on Herbal Medicinal Products
HPLC:	high performance liquid chromatography
i.p.:	intraperitoneal
i.v.:	intravenous
LOD:	limit of detection
LOQ:	limit of quantitation
MDA:	malondialdehyde
MHPG:	3-methoxy-4-hydroxyphenylethylene-glycol
MS:	mass spectrometry
NACE:	non-aqueous capillary electrophoresis
NPD:	nitrogen-phosphorous detector
NP-SH:	non-protein sulphhydryl
NPY:	neuropeptide Y

s.c.:	subcutaneous
TLC:	thin layer chromatography
UHPLC:	ultra high-performance liquid chromatography
UL:	tolerable upper intake level
UPLC:	performance liquid chromatography
UV:	ultra -ultraviolet
Vss:	steady-state volume of distribution