24 September 2025
EMA/HMPC/509423/2023
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Zea mays* L., stigma

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Zea mays* L., stigma
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal substance as herbal tea (decoction) for oral use
Rapporteur(s)	W. Dymowski
Peer-reviewer	I. Chinou

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph public statement on *Zea mays* L., stigma It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

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

- Herbal substance(s) described in pharmacopoeias

There is no monograph for the herbal substance of silk corn in the European Pharmacopoeia. The herbal substance was described in Romanian Pharmacopoeia (Farmacopea Romana Ed A X-A, 1998) as follows: The stigmas of the plant *Zea mays* L. (Poaceae), dried after harvesting. Macroscopic characters. Stigmas in the form of silky, friable, thin, slightly bent, flat, golden-yellow or reddish-brown filaments, 0.5 - 20 cm long and 0.10 - 0.15 mm wide, bifurcated and furrowed on the last 0.4 – 3 mm. Weak, characteristic smell, sweet, mucilaginous taste. The styles and stigmas should be collected from the unripe corn (BHP 1983).

- Herbal preparation(s) described in pharmacopoeias or quality codices

There is no official quality standards established for Maydis stigma preparations in the available pharmacopoeias or codices within the EU countries.

- Relevant constituents for this assessment report

Constituents found in hot water extracts

Carbohydrates/polysaccharides: Current research on fraction soluble in hot water indicates mucilage polysaccharides (Pan *et al*., 2017; Guo *et al*., 2018; Deng *et al*., 2019; Jia Y *et al*., 2021) which is composed of D-mannose, L-rhamnose, D-glucose, D-galactose, L-arabinose, D-xylose and D-galacturonic acid, water soluble flavonoids, tannins (Ammor *et al*., 2019; Limmatrapirat *et al*. 2020). The polysaccharide isolated by Deng et al. (2019) and named SMP-1, was composed of D-mannose, L-rhamnose, D-glucose, D-galactose, L-arabinose, D-xylose, and D-galacturonic acid, with a molar ratio of 1.00:0.21:1.41:1.44:0.70:0.44:0.56 and was mainly bonded by (1 → 6) and (1 → 3) linkages, with various monosaccharides evenly distributed in the main and side chains. Carbohydrates were contained in dry corn silk in 56.2+/-0.7% (Singh *et al*., 2022).

Carbohydrates extractable with ethanol constituted 54.1+/-0.6% of dried herbal substance (Naeem 2022).

Minerals: Corn silk is regarded as a source of potassium salts in the Southeast Asia (Medicinal Plants in Viet Nam 1990). Total ash content not more than 10% (BHP 1983), 8% (BHP 1996), 7% (Romanian Pharmacopoeia 1998); last time determined as 5.3 +/-0.3% in comminuted herbal substance (Singh *et al*., 2022).

Constituents in alcohol extracts

Flavonoid glucosides. Phytochemical analyses of corn silk were stimulated, when in fresh corn silk methanol extract was identified flavonoid maysin, the rhamnosyl-6-C-(4-ketofucosyl)-5,7,3',4'-tetrahydro-flavone (Snook *et al*. 1995) and its reduced derivatives: 3'-methoxymaysin, equatorial 4''-OH-maysin, axial 4''-OH-maysin and axial 4''-OH-3'-methoxymaysin (substances active against corn earthworm larvae possessing also anti-insect properties Waiss *et al*., 1979). Furthermore having analysed alcohol extracts more flavonoids were identified such as: chrysoeriol 6-C-β-fucopyranoside, chrysoeriol, genistein (Suzuki *et al*., 2003a, 2003b, 2007), isorhamnetin (Cao *et al*., 2009); luteolin-3'-methy ether 7-glucuronosyl-(1-2)-glucuronide, -7-O-neohesperidoside, -3'-methyl ether-glucuronosyl-(1-2) glucuronide and -3'-methy ether 7-glucuronosyl-(1-2)-glucuronide (Kim *et al*., 2014) in the

ethanol macerate as well as luteolin glycosides 2''-O-α-L-rhamnosyl-6-C-3''-deoxyglucosyl-3'-methoxyluteolin, 6,4'-dihydroxy-3'-methoxyflavone-7-O-glucoside (Ren *et al*., 2009). Further luteolin derivatives were identified as: 2''-O-α-L-rhamnosyl-6-C-quinovosyl-, -rhamnosyl-6-C-fucosyl-, -L-rhamnosyl-6-C-fucosyl-, -L-rhamnosyl-6-C-3''-deoxyglucosyl-3'-methoxy-luteolin Tian S et al. (2021). Chromen-4-one derivatives and corymboside were identified by Azuvedo et al. (2022).

Phenolic acids. Ethanol extracts contained vanillin, vanillic acid, acetovanillone, 6-methoxy-benzoxazolinone (Suzuki *et al*., 2007), chlorogenic acid (Kim *et al*., 2014), 3-O-feruloylquinic acid, paprazine (coumaric acid derivative), moupinamide (hydroxycinnamic acid derivative) and 3-methoxycinnamic (Azevedo *et al*., 2022). Naeem (2022) found ferulic acid in highest amount in the ethanol extract.

Determination of main phytochemical groups in corn silk of cultivars growing in Serbia shown contents of total polyphenols expressed as catechin 759-2938 mg/100g (0.8 - 2.9%), tannins 638-2498 mg/100g (0.6 – 2.5%); proanthocyanidins expressed as leucoanthocyanidins 75-470 mg/100g (0.07 – 0.5%); flavonoids expressed as rutin 105-1205 mg/100g (0.01 – 1.2%) (Maksimović *et al*., 2005).

Terpenes were found in the volatiles (by steam distillation) of corn silk by El-Ghorab et al. (2007) with main constituents: cis-α-terpineol (24.22%), 6,11-oxidoacor-ene (18.06%), citronellol (16.18%), trans-pinocamphone, eugenol, neo-iso-3-thujanol, and cis-sabinene hydrate; diterpene azulene acetetae derivative (Azevedo *et al*., 2022), macrocarpene sesquiterpenoids and ent-kaurane diterpenoids were identified (Zhou W-Y *et al*., 2023).

Phytosterols were also present (Suzuki *et al*., 2007, Zhang *et al*., 2017) such as: β-sitosterol, stigmasterol, campesterol, stigmast-4-en-3-one, stigmastenone, 7-α-hydroxysitosterol, mainly in ethyl acetate fraction.

Proteins. Singh et al. (2022) has determined 15.29 +/- 1.23 % of proteins in corn silk powder. Ethanol dry corn silk extract from Egypt contained 13% of proteins (Naeem 2022). Orellana-Palacios et al. (2025) tested the corn silk protein fractions obtaining glutelin (67.5%), with higher foaming and thermal properties; albumin (23.2%), with higher *in vitro* digestibility and globulin (9.2%).

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

Not applicable.

1.2. Search and assessment methodology

PubMed search. Bibliography was searched on 18 October 2023 for key words Maydis + stigma in PubMed with results of 35 publications; for Corn + silk with 244 results; for Zea + mays + style with 72 results and for Maydis + stigma + decoction with 135 hits.

Scientific databases

☒ Scientific/Medical/Toxicological databases

Warsaw Medical University databases. Search for "Corn silk" via the library of Warsaw Medical University (23.06.2023) shown 1598 texts, 823 recensed, in following collections: ProQuest Central 1192, Academic Search Ultimate 332, DOAJ 320, Ingenta Content Journals 300, PubMed Central 168, Medium ultimate 148, Springer Online Journal Complete 146, Wiley

Online Library All Journals 136, ScienceDirect Journals 120. Search for "Maydis stigma" via the same library (27.10.2023) shown 94 publications

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (e.g. data from VigiBase, national databases)

☐ Other. No other data

Books

☒ Books referring to the subject are included in chapter 2.2

Regulatory practice

☐ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

☒ Market overview (including pharmacovigilance actions taken in member states)

☒ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☐ Ph. Eur. Monograph

No monograph in the European Pharmacopoeia

☒ Other: Romanian Pharmacopoeia (Farmacopea Romana Ed A X-A, 1998)

Consistency (e.g. scientific decisions taken by HMPC)

☐ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☒ Other: Possible harmonization between other monographs on herbal substances with similar phytochemical and pharmacological profile

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Herbal substance/preparation	Indication	Posology and method of administration	Regulatory status
Zea mays L., stigma	Traditionally in urination disturbances as a diuretic medium.	Herbal tea, decoction. Adults and adolescents from 12 years: pour 1 tablespoon (4 g) of the herbal substance with 1 glass (200 ml) of water, bring to boil and keep boiling for 5 minutes. Drink the glass of fresh	since 11.05.1993, PL

Herbal substance/preparation	Indication	Posology and method of administration	Regulatory status
		prepared decoction 3 times daily, between meals.	
Zea mays L., stigma	Traditionally used to increase the amount of urine and improve urine flow in urinary tract in urination disorders.	Herbal tea, decoction. Adults and adolescents from 12 years: pour 1/2 tablespoon (2 g) of the herbal substance into 1 a glass (200 ml) of lukewarm water, bring to a boil (covered) for 3 minutes. Set aside for 15 minutes, strain and drink the decoction prepared in this way 2-4 times a day in between meals.	since 15.09.1994, PL

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable

Information on other products marketed in the EU/EEA (where relevant)

Not applicable

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

2.1.2. Information on products on the market outside the EU/EEA

Information on the traditional use of corn silk in countries outside of EU is shortly presented as summary of monographs below.

Herbal preparation	**Documented use / Traditional use**	**Posology and method of administration**	**Reference and date of the reference**
Maize silk (styles and stigmas) decoctions, infusions or liquid extract	Maize silk is used as a diuretic in the treatment of heart disease, hypertension, cystitis, urethritis, urinary lithiasis, cholecystitis, hepatitis, rheumatism and diabetes mellitus.	The usual dosage 20 to 30 g per day in the form of decoction, infusion or liquid extract	Medicinal Plants in Viet Nam. WHO 1990
Zea mays L., styles and stigmas, dried herbal substance or by infusion Liquid extract (1:1) Tincture (1:5) in 25% ethanol Syrup in dose 8-15 ml	Cystitis. Urethritis Nocturnal enuresis Prostatitis	Dried herbal substance, 4-8 g, thrice daily Infusions of 4-8 g, thrice daily Liquid extracts (1:1) 4-8 g, thrice daily Tincture (1:5) 5-15 ml, thrice daily Syrup (with the Liquid extract 1 part in 10) 8-15 ml, thrice daily	BHP 1983
Corn Silk as comminuted herbal substance in hard capsules	Maize is used for disorders of the urinary tract (Unproven uses)	Hard capsules, 450 mg	Gruenwald 2007

Herbal preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
Corn Silk for herbal tea, infusion Liquid extract, tincture		Herbal tea, infusion of 2 teaspoons (2-3 g) of drug per cup of water (150-200 mL) Tincture used 2-3 teaspoons a day	
Dried styles and/or stigmas are used as Infusion. Tincture (1:5) in 25% ethanol. Liquid extract of stigmas (1:1) in 25% ethanol	The stigmas and styles of *Zea mays* are used for the supportive treatment of chronic nephritis	*Oral use*. Daily dosage of dried styles and/or stigmas, 4–8 g or infusion (4–8 g in 200 ml of boiling water), one tablespoon three times daily. Tincture, 5–15 ml three times daily. Liquid extract, 4–8 ml three times daily.	WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS) 2010

2.2. Information on documented medicinal use and historical data from literature

Hagers Handbuch der Pharmazeutischen Praxis (Frerichs 1949) described alcoholic preparations: Extractum Stigmatum Maydis and Extractum Stigmatum Maydis fluidum and Sirupus Stigmatum Maydis. Extractum Stigmae Maydis fluidum was mentioned in the fifties in Poland by Roeske (1955). Liquid Extract of Maize Stigmas (according to BPC 1923) and a tincture 1:5 in 25% alcohol were present in British phytotherapeutical bibliography (BHP 1983, BHC 1992, Newall *et al*., 1996; Barnes *et al*., 2007; Veitch *et al*., 2013) but none of the preparations is currently used in the EC countries.

Herbal teas were used in the European countries for many decades as diuretics. Muszyński J (1954) described two Maydis stigma preparations, which were prescribed in the fifties in Poland: infusion of the 30 g of the herbal substance in 500 mL of water and drunken in divided doses during a day and a sirup containing Extractum fluidum Stigmatis maydis 20 g in 180 g of sirupus simplex, used in a single dose a table spoon every two hours. The preparations have been used as a mild diuretic in mild kidney and bladder inflammations. The tradition of use was referred to come from France. Only German authors described the use of low doses of the herbal teas (Gruenwald 2007) as of "unproven use".

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
Stigma maydis, herbal tea, infusion	Used as a mild diuretic in mild kidney and bladder inflammations	Infusion, 30 g in 500 mL, used in divided doses during a day	Muszyński, 1954
Stigma Maydis	Diuretic, soothing the irritated urinary ways mucosa. Used in urinary tract catarrh and urinary tract spasms, nephrosis, urinary tract stones; in insufficient bile secretion	Two tablespoons on half a liter of water for infusion	Informator Terapeutyczny USL, 1959
Maydis stigma, herbal tea, decoction	Diureticum, antispasmodicum, metabolicum, cholagogum	1 tablespoon of herbal substance in a glass of water for decoction. Drink 2-3 times during a day	Gobiec and Konieczny, 1963

Herbal preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
Zea mays L., styles and stigmas, dried herbal substance or as infusion Liquid Extract (BPC 1923) Tincture 1:5 in 25% alcohol Syrup (BPC 1923)	Indications: Cystitis, Urethritis, Nocturnal enuresis, Prostatitis. Specific indication: Acute or chronic inflammation of the urinary system	 4-8 g, thrice daily as a herbal substance *per se* or as an infusion Liquid extract 4-8 ml, thrice daily Tincture 5-15 ml, thrice daily 8-15 ml, thrice daily	British Herbal Pharmacopoeia 1983
Zea mays L., styles and stigmas, dried herbal substance or by infusion Liquid extract (1:1) Tincture (1:5) in 25% ethanol	Dysuria, Cystitis	Dried herbal substance, 4-8 g, thrice daily Infusions of 4-8 g, thrice daily Liquid extracts 4-8 g, thrice daily Tincture (1:5) 5-15 ml, thrice daily	BHC 1992
Corn Silk (Stigma Maydis), comminuted herbal substance Herbal substance as tea, infusion Liquid Extract of Maize Stigmas (BPC 1923) Tincture 1:5 in 25% alcohol Syrup of Maize Stigmas (BPC 1923)	Is stated to possess diuretic and stone-reducing properties. Used for cystitis, urethritis, nocturnal enuresis and specifically for acute or chronic inflammation of the urinary system	Herbal substance 4-8 g for infusion, three times daily Liquid Extract 4-8 ml, thrice daily Tincture 8-15 ml, thrice daily Syrup 8-15 ml (single dose)	Newall et al. 1996
Corn Silk (Stigma Maydis), comminuted herbal substance Herbal substance as tea, infusion Liquid Extract of Maize Stigmas (BPC 1923) Tincture 1:5 in 25% alcohol	Is stated to possess diuretic and stone-reducing properties. It has been used for cystitis, urethritis, nocturnal enuresis and specifically for acute or chronic inflammation of the urinary system	 4-8 g for infusion, three times daily Liquid extract SD 4-8 ml Tincture three times daily	Barnes et al. 2007, Veitch et al. 2013

Infusions used in 1950s in Poland (Muszyński 1950; Informator Terapeutyczny USL 1959) were in a daily dose 30 g of corn silk. Taking into account 2 to 4 daily use of the herbal tea, single doses may be estimated 7.5-15 g. Since the 1960s in Poland were used lower doses, one tablespoon for glass of water as decoction (Gobiec and Konieczny, 1963). The doses of corn silk used for infusion in the British tradition were 4-8 g, thrice daily (British Herbal Pharmacopoeia 1983; British Herbal Codex 1992; Newall *et al*., 1996; Barnes *et al*., 2007).

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal substance/preparation	Indication	Posology and method of administration	Period of medicinal use
Zea mays L.*,* stigma/ comminuted herbal substance	Indications: Cystitis, Urethritis	4-8 g, thrice daily as an infusion	British Herbal Pharmacopoeia 1983); British Herbal Codex 1992; Newall et al. 1996 Barnes

Herbal substance/preparation	Indication	Posology and method of administration	Period of medicinal use
			et al. 2007, Veitch et al. 2013
Zea mays L., stigma/ comminuted herbal substance	Traditionally in urination disturbances as a diuretic.	Herbal tea, decoction. Adults and children from 12 years: pour 4 g of the herbal substance with 1 glass of water, bring to boil and keep boiling for 5 minutes. Drink the glass of fresh prepared decoction 3 times daily, between meals.	Since 05.1993
Zea mays L., stigma/ comminuted herbal substance	Traditionally used to increase the amount of urine and improve urine flow in urinary tract in urination disorders.	Herbal tea, decoction. Adults and adolescents from 12 years: pour approx. 2 g of the herbal substance into 1 a glass of lukewarm water, bring to a boil (covered) for 3 minutes. Set aside for 15 minutes, strain and drink the decoction prepared in this way 2-4 times a day in between meals.	Since 09.1994

Content of herbal substance (comminuted Maydis stigma) in tablespoons, which have been in use during the last 30 years was 3.4+/-0.5g to 4.5+/-0.7g (Dymowski & Jackiewicz 2020) so the average single dose for the 30 years is estimated 4 g. The volume of glass of water used for decoction is estimated 200 ml. The doses of Maydis stigma (corn silk) herbal teas which were been in traditional use over a period of 30 years in the European Union countries were between 8 g (in the British tradition) and 2 g (declared by one manufacturer in Poland) with the average value of 4 g, what correspond to the traditionally used tablespoon for herbal tea infusion or decoction.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

No systematic data available on primary pharmacodynamics.

Maksimović et al. (2004) studied influence on urinary volume and the excretion of sodium, potassium and chloride, 5% and 10% corn silk decoctions which were administered daily to adult male Wistar rats for eight days. The influence of treatment on electrolytes, urea, urinary pH value, creatinine clearance in plasma were observed. Oral administration of 5% decoction at the dose of 10 ml/kg led to a significant and acute diuresis in rats, reaching the peak value in the first 24 h of treatment but application of 10% decoction over a similar period, did not affect urinary excretion of water, however increased the pH value of excreted urine. A significant decrease in sodium and chloride plasma levels was observed in both treated groups. The creatinine clearance was markedly increased after the treatment with both concentrations. The authors concluded diuretic effect of 5% aqueous Maydis stigma extract is in accordance with the increase in glomerular filtration rate and inhibition of sodium

and chloride tubular reabsorption (caused by an unidentified constituent/factor) but not the salt-loading effect.

Pinheiro et al. (2011) studied the effect of aqueous extract of corn silks on the renal flow of water (V) and electrolytes and arterial pressure (AP) in anesthetized Wistar rats. Three groups were tested: intragastric administration (IA) of 1mL of distilled water (negative control); IA of 1 mL of aqueous extract of corn silks at 20%; IA of 1 mL of a furosemide solution (positive control). AP was measured through the left carotid artery, at every 10 minutes, and in the urinary bladder to measure V, at every 30 minutes, and the excreted sodium Qe (Na^+) and potassium Qe (K^+) ions. Experimental protocol covered four periods of 30 minutes each: basal and experimental (Ex) 1, 2 and 3 (30, 60 and 90 minutes after IA, respectively). Group I had no significant differences between periods for the analysed parameters ($p>0.05$). Group II (tested) presented a significant increase ($p<0.05$) in V, Qe (Na^+) and Qe (K^+) in periods Ex2 and Ex3, with significant reduction in AP ($p<0.05$) in Ex2 and Ex3. As expected, Group III (furosemide) had a significant increase in V in periods Ex2 ($p<0.05$) and Ex3 ($p<0.001$), an increase in Qe (Na+) in Ex1 ($p<0.05$), Ex2 ($p<0.001$) and Ex3 ($p<0.001$) and an increase in Qe (K^+) in Ex2 ($p<0.05$) and Ex3 ($p<0.001$), with an important reduction in AP ($p<0.05$) in Ex2 and Ex3. The tested aqueous extract of corn silk has a diuretic effect but does not act as a loop diuretic as it did not lead to marked sodium loss and potassium loss compared to furosemide.

Okunade et al. (2015) investigated the effect of corn silk water extract on serum electrolyte levels. Twenty (20) male albino rats were divided into four groups as; negative control (obtaining normal saline), spironolactone (0.002mg/kg per day) treated (reference) and corn silk aqueous extract in strengths 200mg/kg per day and 600mg/kg per day, treated rats. Blood samples were drawn at baseline, after 10 days and 21days for the estimation of serum Na^+, K^+, Cl^-, HCO_3^-, urea, bilirubin and creatinine. The administration of corn silk extracts for 21 days resulted in a significant ($p<0.05$) increase in serum K^+, HCO_3 and creatinine levels compared with the control. Administration of corn silk extract significantly ($p<0.05$) lowered the serum Na^+ concentrations compared with the control. There were no significant ($p>0.05$) differences in serum urea, bilirubin and serum Cl^-, level between all groups at the end of 21 days.

Solihah et al. (2015) evaluated diuretic effect of a Malaysian corn silk extract in and its dose response relationship in normal Sprague-Dawley rat. Diuretic activity was determined after administration of corn silk extract in doses: 400, 500, 600, 700 and 800 mg/kg. Cumulative urine was significantly increased with the dosage levels (400-600 mg/kg) ranging from 14.06 - 20.13 mL although cumulative urine of aqueous extract of cornsilk (AEC) at 400 mg/kg (14.06 mL) and 500 mg/kg (15.21 mL) treatments was significantly lower than positive control chlorothiazide (10 mg/kg, 21.25 mL). Na^+ urine content was significantly higher compared with negative control at dosages of 500, 600, 700 and 800 mg/kg. At any rate, K^+ and Cl^- content of all AEC treatments were not significantly different during 24 h monitoring. The pH values were increased in parallel to the extract dosages, though it was not significant. As the ED_{50} of the extract was observed at 454.10 mg/kg the authors concluded its mild diuretic activity in elevating urine and Na^+ content at dosages from 500 to 800 mg/kg. The extract also showed an effect of potassium sparing diuretics.

Pardede & Bachri (2018) studied the diuretic effect of corn silk infusion on 30 male rats in 5 concentrations: 2%, 4%, 6%, 8%, and 10%, with positive control furosemide and negative control treated NaCl 0.5 %. The study was focused also on solubility of kidney stones in the excreted urine. The authors observed diuretic effect of corn silk infusions.

Other preparations

Vranješ et al. (2016) tested the effects of corn silk (Maydis stigma) on diuretic activity, electrolytes composition, antioxidant capacity and histopathological features of pretreated mice kidneys. The corn silk group of ten animals drank corn silk extract and water ad libitum. Control animals drank water. On 0, 1st, 7th, 14th and 28th day of the experiment urine volume and electrolyte content were measured, histopathological examination of kidneys was performed at the end of the experiment. On the basis of the overall results corn silk extract was proposed for further investigations as new functional food ingredient with diuretic properties.

Kim et al. (2017) tested influence of corn silk extract (CSE) in BPH symptoms on 6-week-old male Wistar rats, divided into sham-operated control (Sham) and experimental groups. The experimental groups underwent orchiectomy and received subcutaneous injection of 10 mg/kg of testosterone propionate to induce BPH. Testosterone group received only testosterone; Testo + CSE10 and Testo+CSE100 group received testosterone and 10 mg/kg and 100 mg/kg of the corn silk extract respectively. Prostate weight and concentrations of dihydrotestosterone (DHT), 5α- reductase 2 (5α-R2), and prostate specific antigen (PSA) in serum or prostate tissue were determined. In the Testo-Only group, in compared to the Sham group, prostate weight was significantly higher; it was decreased significantly in the Testo + CSE10, and Testo + CSE100 groups ($P < 0.05$), results that were consistent with those for serum DHT concentrations. The concentrations of 5α-R2 in serum and prostate as well as the mRNA expression of 5α-R2 in prostate were significantly lower in the Testo + CSE10, and Testo + CSE100 groups than that in the Testo Only group ($P < 0.05$). Similarly, the concentrations of PSA in serum and prostate were significantly lower in the groups obtaining corn silk extract than in the Testo Only group.

Oyabambi et al. (2020) studied the possible protective effect of corn silk extract on the effect of high salt diet (SD) and on uric acid (UA) production in randomly selected rats in groups (n=5): fed with normal rat feed (CTR), corn silk extract (CS; 500mg/kg), salt diet (8%) and corn silk extract plus high salt feed (SD+CS). After six weeks of feeding each animal was anesthetized and blood samples collected. High salt diet resulted in reduced plasma superoxide dismutase (SOD), nitric oxide (NO) and glutathione peroxidase (GPx) but not endothelial nitric oxide synthase (eNOS); increase in plasma UA and vascular cell adhesion molecule-1 (VCAM-1) the SD group compared with control; increased NO and GPx and not SOD; UA and VCAM-1. The authors concluded that Stigma maydis extract has therapeutic potential in high salt-induced oxidative damage and/or UA-dependent endothelial pathologies.

Almadiy et al. (2021) investigated, on 24 male albino rats (200-250g), divided in four groups (each group consists of 6 animals), influence of corn silk extract (70% methanol, yield 12%) on renal stone formation, hypertension, and observed hepatoprotective effects. The first group of rats took normal diet (served as negative control, Co); the second took normal diet with ethylene glycol (EG) (0.75%) and 1% ammonium chloride (AC) for 28 days and served as positive control (Po). The third and fourth groups took the same substances as in Po group (for induce renal stones) with 200 mg/kg and 400 mg/kg of corn silk (CS) for 28 days respectively. On last day of the experiment blood samples were collected. The tested samples showed a decrease in serum aldosterone hormone, angiotensin converting enzyme, urea and creatinine levels, compared to positive control, significantly decreased AST, ALT, and LDH in comparison to the urolithiatic group and near of normal group. In conclusion, the study confirmed the safety of corn silk extract as anti-hypertensive, antiurolithiatic and hepatoprotective.

Wang et al. (2021) tested *in vitro* two hot water extracted fractions of polysaccharides of corn silk, the neutral (NCSP, Mw 74.1kDa) and acid (ACSP, Mw 109.4 kDa) on its uric acid-lowering activity. Of the two fractions the neutral one NCSP exhibited higher activity in anti-hyperuricemia (HUA). The results

indicated decrease of serum uric acid (UA) and liver xanthine oxidase (XO) activities levels by 45.71% and 22.4% in the NCSP groups, respectively. In addition, NCSP could significantly improve the kidney damage and promote uric acid excretion.

Yuan et al. (2021) tested *in vivo* hypouricemic effect of corn silk flavonoids (CSFs, extracted with hot ethanol) and fractionated on polyamide column with 40% ethanol (CSF-A) and 60% (CSF-B) on a mouse model with potassium oxonate-induced hyperuricemia. CSF-B reduced serum uric acid (UA) level had the best hypouricemic effect, as it decreased the serum UA level by 26.69% and xanthine oxidase (XO) activity in the serum by 11.29%. The mechanism of action of CSF-B was related to the inhibition of XO activity and the promotion of UA excretion. CSF-B contain 12 major flavonoids, five of which were speculated to influence its activity in the hyperuricemia in mice: apigenin-6-C-glucoside-7-O-glucoside, kaempferol-3-O-rutinoside, luteolin-7-glucoside, luteolin-3', 7-di-O-glucoside, and naringenin. Structure analysis revealed that C-4', C5 hydroxyl groups, and C2=C3 double bonds in CSF-B gave its hypouricemic effect.

Gumaih HS et al. (2023) studied antiurolithiatic properties of corn silk extract in twenty-four rats, divided into four groups, the first (negative control), the second (positive control, was treated with 75% of ethylene glycol (EG) and 1% of ammonium chloride (AC) to induce kidney Stones). The third and fourth groups were treated with the same proportions of glycol and ammonium chloride, but with the added corn silk extract in the strengths 200 and 400 mg/kg. After the 28th day, the blood samples and all kidneys of rats from all groups were taken to blood and histological examination. Another ten rats were divided into two groups, group E took a normal diet (negative control), the group F took a normal diet with 500 mg/kg of corn silk extract to investigate its antiurolithiatic effect. The results showed in the corn silk extract group a significant decrease in plasma malonyldialdehyde (oxidative stress marker), serum urea and creatinine. The histological study appeared in the corn silk group fewer CaOx crystals. The authors concluded that corn silk extract acted as an antiurolithiatic drug by increasing urinary pH, diuresis, and was nephroprotective.

Wans EM et al. (2021) investigated the protective effect of corn silk methanolic extract (CSME) against acetaminophen (APAP)-induced nephrotoxicity. The study was carried out on 40 male Wistar albino rats, randomly divided into four groups (n = 10): control group, orally administered with a single dose of 1.8 ml 0.9% normal saline at the last day of the experiment; CSME group, received orally CSME (400 mg/kg bw daily for 5 weeks); APAP group, orally administered with a single dose of APAP (2 g/kg bw); and CSME and APAP group, orally administered with CSME, followed by a single oral dose of APAP. The results of this study revealed that APAP caused a significant increase in serum urea, creatinine level, and malondialdehyde (MDA) concentrations in renal tissues. In addition, APAP caused a significant decrease in superoxide dismutase (SOD) and glutathione peroxidase (GPX) activities in renal tissues compared with the control group. Furthermore, APAP caused marked renal damage as revealed in histopathological architectures alterations of kidney tissues. APAP administration resulted in an expression of caspase 3 and nuclear factor κB (NFκβ) within the renal tubules, caused decrease of proliferating cell nuclear antigen (PCNA) immunostaining and transforming growth factor beta 1 (TGFβ 1) expression within the epithelial lining of the renal tubules. Pre-treatment with CSME restored biochemical parameters, histopathological changes, and immunohistochemical parameters toward normal levels as the control group. In conclusion, oral administration of CSME protected rats against APAP renal toxicity through its antioxidant, anti-apoptotic, and anti-inflammatory protective mechanisms.

Table 5: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
comparable/similar preparations to preparations of the monograph				
Decoction 5 g in 100 mL (5% m/V); decoction 10 g in 100 mL (10% m/V)	Decoctions 5% m/V and 10% m/V administered orally in a dose 10 ml/kg daily	*In vivo* model 24 adult normotensive Wistar rats (200-250 g), divided in 3 groups: distilled water, 5% and 10% m/V corn silk decoctions. Basal level of urine excretion in all 3 groups was established on the first day. Urine samples were collected once daily, before administration of the tested decoctions.	Maksimović et al. 2004	Almost twofold increase of urinary excretion by the 5% m/V corn silk decoction, while 10% decoction showed no influence on the urine volume. The peak level of urine secretion sodium and chlorides secretion was reached after first 24 h and remained stable during the 8 days experiment. In the end of experiment sodium and chlorides in plasma were significantly decreased by the decoction. Oral administration of the decoctions significantly decreased glomerular filtration rate in rats.
Corn silk water extract 20%	Single intragastric administration of 1 mL of 20% corn silk aqueous extract	*In vivo* model on anesthetized rats. Negative control: 1 mL of distilled water Positive control: 1 mL of furosemide solution	Pinheiro et al. 2011	Water corn silk extract increased volume of urine excreted but not led to the sodium and potassium excretion in the same way as furosemide
Corn silk water macerate (350 g in 3500 mL) evaporated to dryness	Oral doses of 200 mg/kg per day or 600 mg/kg per day for 3 weeks	*In vivo* model Effects on serum electrolyte levels in albino Wistar rats (160-190 g). Control obtained oral dose of normal saline. Positive control spironolactone 0.002mg/kg intramuscular injection. Experimental groups obtained oral doses 200 and 600mg/kg per day of the dry extract. Blood samples were taken on day first after 2 weeks acclimatisation for determination of baseline parameters, after 10 days and on the end of experiment, after 21 days	Okunade et al. 2015	21 days administration of the extracts resulted in a significant increase in serum K^+, HCO_3^- and creatinine levels compared with the control. Administration of the extract significantly lowered the serum Na^+ concentrations compared with the control. There were no significant differences in serum urea, bilirubin and serum Cl^-, level between all groups at the end of 21 days.
Corn silk dry powder extracted with distilled water (1:15 w/v) for 30 min. The water macerate filtered and concentrated under vacuum at 60°C and used for the study	Oral doses: 400, 500, 600, 700, 800 mg/kg, in 25 mL of dose preparation	*In vivo* model Male adults Spraque Dawley rats in 7 groups administered with water (negative control), chlorothiazdide 10 mg/kg (positive control). Cumulative 24h urine volume, Na^+,K^+ in urine and osmolality were measured	Solihah et al. 2015	The urine excretion in rats administered with corn silk extract (600, 700, 800 mg/kg) were significantly higher compared with distilled water. Doses 400, 500 mg/kg were statistically lower. Doses 600-800 mg/kg were not different that chlorothiazide 10mg/kg. Na+ excretion was found significantly higher in rats administered with 500-800 mg/kg of corn silk extract but lower than in chlorothiazide. K+ excretion was not different of water. In doses 600-700 mg/kg K+ excretion was lower than in chlorothiazide. The extract did not affect the osmolality (concentration) of urine.

10g, 20g, 30g, 40g, 50g of dried corn silk was infused in 90°C for 15 min. in 500ml of demineralized water and filtered	Oral administration of the corn silk infusions in concentrations 2, 4, 6, 8, 10%. Volumes of administration 2.2-2.7ml.	*In vivo* model Male 30month guinea pigs grouped into 7 groups. 5 groups were administered with corn silk infusions, one positive control furosemide 3.6mg/kg and negative NaCl 0.5%. Urine volumes collected were measured after 1, 5, 24h.	Pardede & Bachri 2018	The urine excretion after 5 hours was markedly higher than in a negative control only in furosemide group. After 24h 10% infusion gave highest urine excretion, higher than furosemide. The infusions in concentrations 2%-8% gave higher urine excretion than negative salt solution but lower than furosemide.
other preparations				
Corn silk ethanol 96% macerate (200g in 4L of solvent) evaporated in vacuo in 40°C	The animals drunk 5% corn silk extract ad libitum. 4 weeks	*In vivo* model For four groups of 10 MLRI albino mice (31-46g) were made available to drink ad libitum 5% solutions of corn silk extract, parsley extract or bearberry leaf extract or water. Urine volume and electrolytes were measured on days: 0, 1st, 7th, 14th, 28th.	Vranješ et al. 2016	In the group of mice dinking corn silk extract solution was seen diuretic effect on the first day of use. Reduction of urea and creatinine.
High maysin corn silk extract (CSE, uncharacterized)	Subcutaneous injection of oil (sham) or testosterone propionate (TS) 10 mg/kg for stimulate BPH in rats. In the experimental groups were injected TS plus finasteride 5mg/kg, CSE 10mg/kg or CSE 100 mg/kg. 6-month observation	*In vivo* model The model of BPH in male rats was induced by single subcutaneous injection of 10 mg/kg testosterone to the orchiectomized rats (*in vivo*) BPH development in testosterone group and in groups administered with counteractive protective substances was and measured prostatic weight	Kim et al. 2017	Prostate weight in the end of experimental group was lowest in the untreated animals. Among the groups treated with testosterone high maysin corn silk extract in both concentrations and finasteride significantly lowered prostate weight in rats
50g of corn silk was dried, extracted with 200ml of methanol and dried.	The extract was redissolved in DMSO to 200mg/ml, filtered and administered at a dose 500mg/kg. 6 weeks	*In vivo* model 20 female Wistar rats (mean weight 135g) were acclimatized and randomly allotted to 4 groups: control fed with normal diet, corn silk extract 500mg/kg, high salt diet, and high salt diet with plus corn silk extract. After 6 weeks the animals were sacrificed. and blood samples were collected by cardiac puncture. Biochemical assays of plasma cell adhesion molecule (VCAM-1), nitric oxide, uric acid were determined by using ELISA kit.	Oyabambi et al. 2020	Significant increase in plasma cell adhesion molecule -1 in high salt diet group while was significantly attenuated in corn silk extract and salt diet plus corn silk extract group. Administration of the extract reduced plasma uric acid which was experimentally elevated in the high salt diet group.
Dry comminuted corn silk extracted successively with 70% and 30% methanol (DER 8.3:1) evaporated to powder	200, 400mg/kg corn silk extract, oral administration	*In vivo* model 24 male Wistar albino rats (200-250g), divided in 4 groups. 1st negative control, 2nd on normal diet with induced kidney stones (ethylene glycol 0.75% and 1% ammonium chloride), 3rd and 4th with induced	Almadiy et al. 2021	Observation of increase of aldosterone level in the urolithiatic group; decrease in serum aldosterone hormone, ACE, urea and creatinine in corn silk extract groups in compared to the control

		kidney stones and 200, 400mg/kg corn silk extract, for 28 days. After the exposure in blood samples were estimated: serum aldosterone, angiotensin converting enzyme (ACE); liver aminotransferases (ALT, AST); creatinine and urea.		
Dry corn silk extracted by water in 80°C (1:100 w/V) for 1.5 h, lyophilized, purified on DEAE-52 column to obtain two polysaccharide components (neutral and acid), with molecular weight determinated	Oral administration of polysaccharide fractions NCSP and ACSP (20mg/kg). 7 days	*In vivo* model. Male Kunming mice (20g) were randomly divided in 4 groups (n=8): normal control, hyperuricemia model group (established by potassium oxonate once daily for 7 consecutive days), NCSP and ACSP. One hour after the oxonate administration mice from normal control and model group received normal saline, NCSP and ACSP (20mg/kg)	Wang et al. 2021	Two neutral and acid polysaccharides (NCSP and ACSP) with 74 and 109 kDa. The NCSP have anti hyper-uricemic activity, promoted uric acid excretion
Ethanol extract (in 70°C (1:40) (w/V), lyophilized and fractionated on polyamide. Fraction CSF-A contained mainly rutin, quercetin, apigenin, kaempferol. Fraction CSF-B mainly rutin, luteolin and kaempferol	Oral administration 20mg/kg. 7 days	*In vivo* model. Male Kunming mice (20g), five groups (N=8): normal control, hyperuricemia, AP, corn silk flavonoids fractions A and B. Model hyperuricemia established by potassium oxonate. Mice of normal control received normal saline, of the other groups oxonate for 7 days to induce hyperuricemia. Those of AP, flavonoid A and B obtained 5mg/kg of allopurinol and those of flavonoid groups additionally 20mg/kg of flavonoids A or B.	Yuan et al. 2021	Fraction CSF-B had the best hypouricemic effect, reduced serum uric acid and promoted its excretion
Corn silk dry powder extracted successively with 70% and 30% methanol (DER 8.7:1)[11.5% yield] evaporated to powder	Oral administration of 200, 400mg/kg corn silk extract to animals with induced kidney stones, for 28 days	*In vivo* model. 24 male Wistar albino rats (200-250g), divided in 4 groups. 1st negative control, 2nd on normal diet with induced kidney stones (ethylene glycol 0.75% and 1% ammonium chloride), 3rd and 4th with induced kidney stones and 200, 400mg/kg corn silk extract, for 28 days. At the end blood samples were taken for assessing malonyl-dialdehyde, serum urea, creatinine, urinary pH, Mg and citrates. 20 additional animals, divided in two groups: E normal diet a negative control, F normal diet + corn silk extract 500mg/kg for histopathological studies	Gumaih HS et al. 2023	Significant decrease of malonyldialdehyde, urea, creatinine in plasma; increase of urinary pH, urinary Mg and citrates in the treated group. Histopathological study appeared fewer CaOx crystals.
Corn silk powdered macerate (250g)	Oral administration of dose	*In vivo* model. 40 male albino trats divided in 4 groups: active group	Wans EM et al. 2021	In the corn silk 5-week pretreated group of animals the symptoms caused by single

with 1L of MeOH 80%, evaporated to yield 12% (8.3:1)	400mg/kg of corn silk methanol extract.	administered with 400 mg/kg of the corn silk extract for 5 weeks; active group pre-treated with 400 mg/kg of the corn silk extract 400mg/kg for 5 weeks and at the last day added acetaminophen (APAP) 2g/kg; positive control group obtained at last day 2g/kg acetaminophen for induce nephrotoxicity; negative control administered with normal saline. The authors compared effects caused by single administration of 2g/kg acetaminophen to rats: increase in serum urea, creatinine, malondialdehyde; decrease in superoxide dismutase (DOD), glutathione peroxidase (GPX); histological renal tissues alterations; renal tissue alterations, expression of caspase 3, nuclear factor NFκB, PCNA; immunostaining and transforming growth factor beta-1 (TaFβ1) in renal tubules.		administration of acetaminophen were reversed

Assessor's comment:

There are published studies on corn silk water extracts (Maksimović *et al*., 2004; Pinheiro *et al*., 2011; Okunade *et al*., 2015; Pardede & Bachri 2018) but the results of the experiments are not fully coherent. The first publication by Maksimović *et al*., 2004, where the herbal preparation was adequately described, have no positive control to compare its possible mechanism to any pharmacological model and the results of two tested doses were not dose dependent; only 5% w/v decoction was found diuretic. In the second publication the preparation (water solution) was compared to the furosemide, but the observed effect was referred to be not the same as of the comparator. For higher doses of concentrated corn silk macerate Okunade *et al*., (2015) described the effect as 'spironolactone-like'. Solihah *et al.*, 2015 observed diuretic effect higher than negative control but much lower than chlorothiazide's. Pardede & Bachri 2018 compared diuretic effect of corn silk infusions to furosemide in guinea pigs, but it was found slower needed higher strengths. Almadiy (2021) and Gumaih (2023) observed also potassium retention effect of dried alcohol corn silk extracts in rats.

3.1.2. Secondary pharmacodynamics

Nephroprotective effect

Nwachuku et al. (2020) observed nephroprotective effect of corn silk water extract in doses 200 and 400 mg /kg per day administered to male albino rats with gentamicin-induced nephrotoxicity (80 mg/kg per day for 7 days). Treatment the animals after a week exposure for gentamicin followed by the treatment with a corn silk extract gave positive effects both in lower and higher corn silk extract doses. The results obtained suggested protective potentials of corn silk extract on gentamicin-induced

nephrotoxicity in albino rats, but the therapeutic effects were progressively gradual and not so fast in effectiveness.

Neuroprotective effects

Ryuk et al. (2022). The extracts examined if the corn silk water extract (1:10 w/v), in Mongolian gerbils, administered with (0.05%, 0.2% extract, v.0.02% aspirin as an antiischemic control) could alleviate ischemic stroke symptoms and post-stroke hyperglycaemia. The gerbils underwent an artery occlusion for eight minutes and reperfusion and then were fed with the assigned diet; those without artery occlusion, having the same diet. Corn silk extract intake reduced neuronal cell death in gerbils with ischemia and reperfusion (I/R) and dose-dependently improved neurological symptoms, the short-term memory and spontaneous alteration and grip strength compared to the I/R-control group, with the reduced tumour necrosis factor-α, interleukin-1β, superoxide, and lipid peroxide levels, promoting superoxide dismutase activity in the hippocampus in the extract groups, compared to the I/R-control. The blood flow measured by Doppler was improved in the extract group compared to the I/R-control. For the neuroprotective activity of the corn silk extracts are suspected macrocarpene-type sesquiterpenes (Zhou *et al*., 2020).

Hepatoprotective effects

Naeem (2022) observed administration of dry corn silk extract powder, the ethanol extract (10 g in 100 ml of ethanol) and a tea, to rats (5 groups, 6 animals each). The increases of body weight gains in groups administered with the tea, dry ethanol extract and corn silk powder were 5.3, 9.3 and 5.7% while gentamicin 1.1%. (positive control). Serum levels of urea, creatinine and uric acid were significantly decreased in groups administered with corn silk powder, corn silk tea and corn silk extract. The corn silk ethanol extract, the tea and powder demonstrated significant decrease of gentamicin increased liver enzymes (ALT, AST, ALP) by 95, 209, and 318 µ/l in compared to the positive control.

Influence on lipid balance and possible antiobesity activity

Lee et al. (2016) and Cha et al. (2016) studied influence of high maysin corn silk extract (no further information) on body weight and fat deposition in C57BL/6J mice fed with high-fat diet. The normal-fat diet mice received 7% (w/w) and the high-fat 25% and 0.5% of cholesterol and the high-fat corn silk extract group received additionally 100 mg/kg of the high maysin corn silk extract. During the 8 weeks study were measured: body weight, body fat, mRNA expression levels of proteins involved in adipocyte differentiation, fat accumulation, fat synthesis, lipolysis, and fat oxidation in adipose tissue and the liver. The authors concluded that the extract inhibited expression of genes involved in adipocyte differentiation, fat accumulation, and fat synthesis as well as promotes expression of genes involved in lipolysis and fat oxidation, further inhibiting body fat accumulation and body weight elevation in experimental animals. Addition of the high maysin corn silk extract improved adipocytokine secretion, decreased the regulatory pool of cholesterol in line with its blood and hepatic level; also improved glucose homeostasis.

In the Traditional Oriental Medicines, in Vietnam and TCM, corn silk teas were used for diabetes and as an antiobesity medium so as a number of pharmacological works have been published, being outside the scope of the traditional use legislation in Europe.

Potential antidiabetic properties

Suzuki et al. (2005) observed that administration of Maydis stigma hot water extract (2kg extracted with water in 80°C for 2 h, lyophilized with yield 160g) prevented diabetic glomerular hyperfiltration and supressed progression of diabetic glomerular sclerosis in the experimental model of diabetic nephropathy induced by streptozotocin (40mg/kg) in Wistar rats. Zhang et al. (2013) found that a

polysaccharide water extracts of Maydis stigma (500g, distilled water, 1:30), deproteinated, in mouse with established diabetes 1 and 2 models, administered 3-4 weeks, significantly lowered blood glucose level and diabetes symptoms in compare metformin (50 mg/kg), with significant improvement of symptoms of type 1 diabetic mice. Zhang et al. (2016) found also the ethanol flavonoid extract, in doses 300 and 500 mg/kg significantly reduced blood glucose level, body weight loss and water consumption in streptozotocin-induced diabetic mice model and lowered: cholesterol, triacylglycerols, LDL-C fraction. Wang et al. (2016) administered isolated polysaccharides fraction to the Kunming diabetic (streptozotocin) mice in doses: 400, 600, 800 mg/kg; with blank control and positive control with dimethyl-biguanide 600mg/kg) for 5 weeks. The groups treated with polysaccharides showed significant ($p<0.01$) differences in body weight, depression etc., from the third week and blood glucose significantly lower than in the streptozotocin diabetic mice.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Traditional use monograph

The available non-clinical data on Maydis stigma water extracts activity supports the plausibility of proposed traditional use as a diuretic mean.

The available data, although not systematic, are repeatable in the area of influence on quantity of excreted urea. The mechanism of diuretic effect of concentrated water extract (used as decoction), which was suggested to be potassium saving, need further studies for confirmation.

The available non-clinical data seems to be consistent to the data on traditional use.

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

As there is no pharmacokinetic model for herbal tea, decoctions, the data are not available.

Assessor's comment:

Although pharmacokinetic model on rats, was published for ethanol extracts, containing mainly flavonoids, but it has rather limited applicability to the herbal teas which are the available on the pharmaceutical markets.

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

3.3.1. Single dose toxicity

Water corn silk decoction extract acute toxicity study (Ikpeazu *et al*., 2018)

Water macerate prepared of 100 g of corn silk in 1000 ml of distilled water and declared to be boiled for 4 h, filtered and dried. The concentrated dry extract was reconstituted with distilled water to doses

500, 1000, 2000 mg/kg, up to the 5 g/kg was used in the study. Oral acute toxicity test was carried (according to OECD guideline) on Wistar rats (150-170 g) randomly divided into five groups of 12 animals (6 males and 6 females). The tested doses were administered by oral gavage, the control received 0.5 ml of water and were monitored for behavioural changes and signs of toxicity for 24 h and thereafter for 14 days. The LD_{50} of Stigma maydis boiled water extract in male and female rats was greater than 5 g/kg.

Water corn silk extract ethanol flavonoid fraction (flavonoid-rich extract of Maydis stigma, FMS) (Peng *et al*., 2015).

300 g of the powdered corn silk was extracted twice with 4.5 L of water at 80°C. The extract was concentrated to 3 L in a rotary evaporator in 40°C and precipitated with anhydrous ethanol to a concentration 70%, centrifuged and the supernatant concentrated, and freeze dried to obtain flavonoid-rich extract. The extract was suspended/redissolved in water, extracted with petroleum ether and then partitioned with ethyl acetate to separate flavonoids and evaporated (contained 10.45% of flavonoids by spectrophotometric method). The mice (weight of 18 to 22 g) were randomly divided into 2 groups, the control group and experimental group, each group had ten mice with half male and half female. Experimental groups were orally administered with a 3-doses (each of 10 g/kg) in the distilled water by oral gavage; the control group was administered with the equivalent of distilled water. This way all the tested mice obtained a maximum daily dose up to 30 g/kg body weight. Then the groups were observed for 14 days for clinical signs like body weight gain, food, and water consumption and mortality. On day 14 on completion, all the animals were euthanised and blood samples were collected from mice for biochemical parameters determination: glucose (GLU), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST). The main organs (heart, liver, spleen, lung, kidney, thymus, brain, bladder, uterus, testis, epididymis, seminal vesicle) were removed, dried and weighed. The median lethal dose (LD_{50}) values were determined according to the test results. During a 14-day observation period, there were no abnormal signs in any of the groups, which included addition of body weight, as well as food and water consumption. The extract solutions at the dose of 30 g/kg did not cause the death of male and female mice over 14 days. The results indicated the oral lethal dose (LD_{50}) value for oral administration of the flavonoid fraction (FMS) in male and female mice is higher than 30 g/kg.

Corn silk ethanol purified extract (Ha *et al*., 2018).

The data are available for corn silk extract prepared with ethanol 99% (1 kg of the herbal substance + 2 L of the extraction solvent), later underwent to the removing chlorophyll (with methylene chloride and polar carbohydrates and polyphenolic compounds (on C18 column). 14-day test with 2 g/kg the described extract shown no mortality, no difference between body weight between control mice and the administered with the extract.

Corn silk ethanol liquid extract (Abudayeh *et al*., 2022).

Corn silk was purchased from local market in Amman, Jordan, authenticated in Biodiversity Dep. National Research Center Amman, Jordan. The raw material was washed in a tap water, dried in an air-shadowed environment, when dry comminuted to the 3 mm particles and stored in airtight vials. The liquid extract was prepared on a base of earlier extraction efficacy of the herbal substance and ethanol 40% (1:1). Rats of both sexes (male 164.3+/-5.4g; female 160.0+/-4.2g) were administered (intragastric) with growing doses of the liquid extract: 2, 2.5, 3.1, 3.9, 5, 6.3, 7.9, 10.0 ml. With an increase of the doses exacerbated the symptoms of poisoning: excitation, 10 min after administration with subsequent change in inhibition of motor activity, gradual loss of appetite and decrease response to the stimuli. The deaths were observed mostly in the first two days after single dose administration.

The average lethal doses were established for males 5.15 ml/kg and females 5.64 ml/kg. There were no visible changes in the internal organs, its colours, the lungs retain specific structure, the size and mass of the internal organs do not change significantly.

Assessor's comment:

There is no data on the herbal tea infusions or decoctions. The effect of the corn silk water macerate in rats was not established. LD50 higher than 5 g/kg.

Corn silk ethanol liquid extract, (1:1) with 40% ethanol, administered orally to rats showed LD50 for males 5.15 ml/kg and females 5.64 ml/kg.

Flavonoid fraction, free of solvents, showed LD50 in mice higher than 30 g/kg as a daily dose.

3.3.2. Repeat dose toxicity

Herbal substance (Wang *et al*., 2011)

Corn silk (from *Zea mays* L., cv. Zhang Dan 958) powdered was added to the standard granulous diets. The 90-day toxicity was observed on 80, four-week-old, 40 male and 40 female Wistar rats. Before inclusion the animals were examined for a behaviour and acclimatized during 7 days and randomized into the four groups: the control and administered with 0.5%, 2%, 8% corn silk in a feed. The observation (twice daily) included coat condition, mucus membranes, occurrence of secretions and excretions, autonomous nervous system reactions, changes in gait, posture, clonic, tonic bizarre. Visual examination before the access and over the 12 weeks (eyeball position, conjunctivas, corneas; body weight and food consumption were determined every week. At termination two blood samples were collected, to haematology and serum chemistry. Haematological examinations: white blood cells (WBC), red blood cells (RNC), haemoglobin (HGB), haematocrit (HCT), blood platelet count (PLT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell volume distribution (RDW), lymphocytes (LY), monocytes (MO), granulocytes (GR). Serum chemistry: blood urea nitrogen (BUN), creatinine (Cr), blood uric acid (BUA), blood glucose (Glu), triglycerides (TG), total cholesterol (TCH), total protein (TP), albumin (Alb), globulin (Glb), alanine transaminase (ALT), aspartate transaminase (AST), alanine phosphatase (ALP). At termination visual inspection of gross pathologies was conducted: surfaces, orifices, cavities (cranial, thoracic, abdominal, pelvic). Organs: cerebrum, cerebellum, thyroid, thymus, heart, lung, liver, spleen, kidney, adrenal gland, pancreas, bladder, ovary, uterus, testes, epididymis seminal vesicles and prostate were excised and weighed (thyroids, prostatae uterus only after fixation). Paired organs were weighed as a total or left and right with relative weight. Selected tissues from 8% group and a control were fixed and stained for histopathological examination. Results: Clinical observations didn't show treatment-related signs of adverse effects in clinical appearance; body weight increased gradually without of statistically significant differences between food consumption in the groups 0%, 0.5%, 2%, 8%: 32.68 ± 6.8, 32.3 ± 7.5, 35.1 ± 10.0, 35.0 ± 11.2 for males, and 24.8 ± 3.6, 26.6 ± 6.7, 25.9 ± 5.7, 25.1 ± 5.2 for females (females consumed higher amounts of corn silk). There were no treatment-related adverse effects of corn silk on haematology parameters in females and males. In serum analysis of 0.5% females TP and globulins were higher than the mean values in control group. Also, higher creatinine and BUA were observed in 0.5% males (72.1, 73.8), than in the control (61.7 and 37.8). According to the results, changes were found only in one sex and were not considered to be of toxicological relevance. The serum biochemistry analysis indicated that feeding a diet containing corn silk at doses up to 8% to rats for 90 days had no adverse effects. No treatment-related changes with toxicological significance in relative organ weights were noted in females and males following

administration of corn silk. The few findings observed were consistent and stay within normal background lesions in clinically normal rats of the age. The NOAEL was estimated with 8% of corn silk in a diet in Wistars male and female rats were 9.3 and 10.3 g/kg per day respectively.

Corn silk water extracts

Corn silk water extract haematological evaluation (Saheed *et al*., 2015)

The material was harvested from maize plantation (Malete, Ilorin, Nigeria, between April and August 2014 and was authenticated and deposited in Kwara State University, Ilorin, Nigeria). Corn silk was dried in a shadow and powdered with a blender. 400 g of the powdered substance was suspended in 4 L of distilled water macerated for 48 h with regular shaking, filtered and lyophilized to give 22.5 g residue with yield 5.6% (DER 17.8:1). The lyophilizate was reconstituted in water to give doses 100, 200 and 400 mg/kg/bw. 100 of Wistar rats (150-180 g), randomised into 4 groups, were used for the study. Group 1 administered with 1 ml of distilled water served as a control. Groups 2-4 administered with 100, 200, 400 mg/kg b.w. of the extract via oral intubation. Animals were kept in temperature 25+/-2°C, with 12h light/dark cycle, and were allowed to food and water ad libitum. 25 of all of the group were sacrificed 24 h after extract administration on days: 1, 7, 14, 21, 28 and 2 ml blood samples were collected to analyse haematological parameters in a automated haematologic analyser. Administration of the extract in the tested doses had no significant ($p>0.05$) effect on the haemoglobin, haematocrit, red blood cell (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and mean platelet volume (MPV). Except for the first day the extract significantly increased WBCs in compared to the control. In the groups administered with the corn silk extract was observed significant growth in lymphocytes ($p<0.05$) in compared to the control. The platelet counts significantly increased in a highest dose 400 mg/kg b.w. The feed and water intake by the extract-treated animals increased in all doses throughout the experimental period. At all the extract groups investigated, significant decrease in the serum level of total cholesterol and triacylglycerols was recorded. Administration of the extract also revealed a significant reduction in atherogenic index (ratio of LDL-C/HDL-C) across all groups by the corn silk extracts.

Water corn silk macerate subchronic toxicity (Ikpeazu *et al*., 2018).

Four groups of six male rats received: 0.25 ml of water, 500, 1000, 2000, 5000 mg/kg of the water corn silk (purchased from Eke Okigwe market in Okigwe, Imo state, Nigeria, in June 2017). The herbal material was declared to be macerated (100 g of corn silk in 1000 ml of water) then boiled for 4 h in 100°C and evaporated. The final extract was administered to rats for 28 consecutive days. After the experiment the rats were euthanized under anaesthesia and blood samples were collected to haematological parameters for measure the samples of organs; liver and kidney were taken for histopathological testing. In the sub-acute study, the extract caused an observable significant increase ($p < 0.05$) in triglycerides (TAG), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL), while the concentration of high-density lipoprotein (HDL) decreased significantly ($p < 0.05$) when compared to the control group. AST and ALT increased significantly ($p < 0.05$) in rats treated with 1000 and 2000 mg/kg of Stigma maydis compared to their control. The histopathological results revealed degenerative changes in the liver at 2000 mg/kg body weight extract. In long term treatment, toxic effects were observed in liver at the doses of 1000 and 2000 mg/kg. This study suggests that prolonged use of higher doses of aqueous extract of Stigma maydis ≥ 1000 mg/kg could be hepatotoxic.

Assessor's comment:

Water corn silk macerates of the herbal substance from open market in Africa, which were administered for 28 days to male rats, were found to be safe only in dose 0.5 g/kg. The macerate administered to rats in dose of 1 g/kg, was observed hepatic enzymes increase and at the dose 2 g/kg hepatotoxic changes so the authors advised only the lowest dose (0.5 g/kg) for use. Water macerates, followed by heating, are not used because of because of possible development of microflora, possible pollution with microflora and mycotoxins. The hepatotoxic constituent was not identified in this study. In contrast to this experiment with a macerate, the water extract which was deproteinised with ethanol and fractionated in the direction of flavonoids, was safe for male and female mice until the dose of 10 g/kg (NOAEL), see below Peng 2016 below. Also, herbal substance in 90 days toxicological assessment in Wistars male and female rats have NOAEL 9.3 and 10.3 g/kg per day, see Wang 2011 above.

Flavonoid extracts

Ethanol flavonoid fraction of water corn silk extract (flavonoid-rich extract of Maydis stigma, FMS). Subchronic toxicity (Peng *et al*., 2016).

300 g of the powdered corn silk was extracted twice with 4.5 L of water at 80°C. The extract was concentrated to 3 L in a rotary evaporator in 40°C and precipitated with anhydrous ethanol to a concentration 70%, centrifuged and the supernatant was concentrated and freeze dried to obtain flavonoid-rich extract. The flavonoid-rich extract was suspended/redissolved in water, extracted with petroleum ether and then partitioned with ethyl acetate to separate flavonoids and evaporated. The main constituents of the ethyl acetate extract were rutin, apigenin and diosmetin. Subchronic toxicity was observed on Kunming mice (25-30 g). As the previous study indicated acute toxicity LD_{50} in mice higher than 30 g/kg, three doses were selected for subchronic testing: 2.50 g/kg as low dose, 5.00 g/kg as mid dose and 10.00 g/kg as high dose. 80 mice were randomly divided into 3 treatment groups and a control group, and each group had 20 mice with half males and females. The extract was administered by gavage for 28 days and on day 29 all mice were anesthetised, blood samples were collected for haematological parameters measuring and organs (brain, thyroid, thymus, heart, liver, spleen, kidney, adrenals, stomach, duodenum, colon, pancreas, mesenteric, lymph node, bladder, testes/ovaries) were examined for macroscopic pathological changes and relative organ weight was calculated. The organs were fixed for histopathology examination. All the animals survived all the 28 days period, even in high dose 10 g/kg. There were no statistically significant differences in body weights between the extract and control group. The feed consumption was slightly decreased in the extract group, but the difference was not significant. No significant differences were observed in haematological and serum biochemical parameters on the day 29. Microscopic observations revealed no pathological changes associated with the administration of the extract. No changes were observed in the livers and kidney, heart, spleen, lung, stomach, testis and ovaries from any of the groups. In conclusion, subchronic oral administration of FMS showed the no-observed-adverse-effect level (NOAEL) of FMS is 10 g/kg per day for both male and female mice.

Ethanol corn silk extract subacute toxicity study

Ha et al. (2018) studied subacute toxicity of corn silk extract (contained high level of maysin, no more data available) orally administered to mice over a 4-week period in doses 0 and 2000 mg/kg b. w., water and food consumption, and organ weight were measured, and urine and serum were analysed. Body weights did not show any significant change compared to those of the control group. Lethal dose of corn silk extract was estimated to be more than 2000 mg/kg. In the 4-week subacute toxicity study, there was no corn silk extract related toxic effect on body weight, water intake, food consumption, urine parameters, clinical chemistry, or organ weight. Histopathological examination showed no abnormality related to the administration of corn silk extract at 500 mg/kg. The observed non-toxic dose of the corn silk extract was found to be more than 500 mg/kg.

3.3.3. Genotoxicity

No data are available on corn silk water extracts mutagenicity tests *in vitro* on Salmonella strains.

Micronucleus assay of water corn silk extract ethanol flavonoid fraction (flavonoid-rich extract of Maydis stigma, FMS) (Peng *et al.*, 2016). Fifty mice, half male and female, randomly divided into five groups. The extract was administered by oral gavage in distilled water at doses: 2.50, 5.00 and 10.00 g/kg for 2 days at 24 h intervals. Cyclophosphamide 40 mg/kg was given to mice as positive control, distilled water as negative control. 6 hours after treatment bone marrow was collected from bone marrow and diluted with calf serum. The cell suspensions were smeared onto slides, dried, fixed with methanol, stained with Giemsa. The number of micronucleated polychromatic erythrocytes (PCE) was counted based on examination of 1000 PCE of each animal and the frequencies of micronuclei per thousand and the ratio PCE to red blood cells was calculated based on an examination of 1000 red blood cells (RBC) per mouse. There were no statistically significant differences in the PCE/RBC ratio and the micronucleus frequency between each FMS-treated groups and negative control group ($p<0.05$), which indicated that the extract FMS shows no genotoxic activity in bone marrow stem cells at doses of up to 10 g/kg bw.

Table 7. Genotoxicity study

Type of test/reference	**Test system**	**Herbal preparation**	**Concentrations/Concentration range/ Metabolising system**	**Results/Positive/negative/ equivocal**
Chromosomal aberrations *in vivo*. OECD Guidelines for the Testing of Chemicals, Test Guideline 475, 1997 Peng et al. 2016	Mammalian Bone Marrow Chromosome Aberration Test (Micronucleus assay).	300 g of the powdered corn silk was extracted twice with 4.5 L of water at 80°C. The extract was concentrated to 3 L in 40°C and precipitated with anhydrous ethanol, centrifuged and the supernatant concentrated, and freeze dried to obtain flavonoid-rich extract. The extract was redissolved in water, extracted with petroleum ether and then partitioned with ethyl acetate to obtain flavonoid dry fraction	The extract was administered orally, dissolved in distilled water to fifty mice of both sexes, at doses: 2.50, 5.00 and 10.00 g/kg for 2 days at 24 h intervals	There were no statistically significant differences in the PCE/RBC ratio and the micronucleus frequency between each extract treated groups and negative control group. The extract showed no genotoxic activity in bone marrow stem cells at doses of up to 10 g/kg

Assessor's comment:

There are no available genotoxicity data on herbal tea, decoctions and raw water extracts.

The available data from micronucleus assay of water corn silk extract ethanol flavonoid fraction (free of polysaccharides and proteins) have limited relevance to the products which have been traditionally used in Europe and are available on the market.

3.3.4. Carcinogenicity

No data available

3.3.5. Reproductive and developmental toxicity

Sperm malformation assay of water corn silk extract ethanol flavonoid fraction (flavonoid-rich extract of Maydis stigma, FMS) (Peng *et al*., 2016)

Fifty adult males were randomly divided into five groups. The extract was administered by oral gavage in doses: 2.50, 5.00 and 10.00 g/kg for 5 days with 24 intervals. Mitomycin C 1.5 mg/kg and distilled water were given to mice for 5 day as positive and negative controls. All animals were maintained on basal diet for 34 days and sacrificed on the 35th day after the first treatment. The epididymies were dissected, cut into pieces, stirred, centrifuged and used for preparation of slides stained with eosin. The number of spermatozoa with morphological abnormalities was counted based on an examination of 1000 spermatozoa per animal under a microscope, and the sperm malformation rate was calculated. There were no statistically significant differences in sperm malformation rate between the FMS-treated groups and negative control group ($p<0.05$) what indicated that the sperm malformation rate was not significantly affected by the extract.

3.3.6. Local tolerance

No data on topical use are available.

3.3.7. Other toxicity studies

Cardiotoxicity of the aqueous extract of corn silk in rats (Adedapo *et al*., 2015).

Water macerate, prepared of corn silk (in unknown quantity) in 1000 ml of water, was administered in rats in doses 200, 400 and 800 mg/kg, plus control received 3ml/kg of distilled water, for seven days. On the eighth day the authors recorded electrocardiograms in animals, in ketamine/xylazine-induced anaesthesia, to determine changes in the heart rate (P-wave duration, P-R interval, R-amplitude, QRS duration, QT interval and QTc) and hearts from the experimental animals were collected for histopathological changes. The authors observed a significant change in the heart rate (groups B and C), P-wave duration (group D), QT interval (groups B, C and D) and QTc (groups B, C and D), in compared to the control group. Histology also showed, in the sections of the heart, fatty infiltration of inflamed heart and areas of moderate inflammation of the atrium and ventricle.

Assessor's comments:

1. Quantity of the corn silk which was used extracted in 1000 ml of water was not declared in the publication, so its concentration is not known.

2. There is not report on any toxic substance contained in the corn silk as such. Although, corn silk containi carbohydrates and proteins fresh material is susceptible to bacterial and fungal infections. Corn pollutions w mycotoxins like zearalenone and nivalenol are known (Munkwold 2019; Vincelli and Parker 2019) and reflec in the EFSA opinions on the risk (2011, 2013). Taking it into account the maceration is not used traditionall European countries, instead are used infusions or decoctions.

3. Histopathological changes (fatty infiltration of inflamed heart) observed after one week of this experiment may reflect the exposure of animals for any substance with quick toxicodynamic or the use of infected animals. The changes observed in electrocardiograms in animals suggest exposure to intensive cardiotoxic unidentified factor contained in the tested preparation or food. Also, the influence of ketamine or xylasine on heart in the experiment or pesticide pollution can't be excluded. The published result of this experiment (Adedapo *et al*., 2015) can't be conclusive. Further studies and clarifications are required. According to the ICH S7B guidance (p.3.1.), the experimental system should have been validated.

3.3.8. Conclusions on toxicological data

Non-clinical information on the safety for *Zea mays* L., stigma, herbal tea, infusion or hot water extracts is scarce. There are no systematic toxicological data available for herbal tea preparations which are used in the European Union countries. The preparations described in the publications differs in methods of preparation and in phytochemical content. Also, methodologies of toxicological tests used for safety assessment were sometimes different than in EU or ICH guidelines.

Two publications on one week toxicity testing of corn silk macerates showed differences with other results but their hygienic conditions of preparation were essentially different than of infusions or decoctions used in the Europe.

The herbal substance does not contain constituents with safety concerns. There are no genotoxicity data on herbal tea decoction or crude corn silk hot water extract. The available data are limited only to ethanol flavonoid fraction of the water extract. The fraction in micronucleus assay shows no genotoxic activity in bone marrow cells at doses of up to 10 g/kg bw (Peng *et al*., 2016).

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on reproductive toxicity, further tests for genotoxicity and carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant non-clinical pharmacology studies on *Zea mays* L., stigma, are limited and not required.

The main non-clinical pharmacological effects of urine and sodium increase in *in vivo* experiments were shown for *Zea mays* L., stigma, water extracts, comparable to preparations of the monograph. Results from relevant experimental studies to support the proposed indications are limited.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of *Zea mays* L., stigma, preparations is scarce.

With the limited data available it is difficult to draw any firm conclusions especially regarding genotoxicity, carcinogenicity, and reproductive and developmental toxicity. Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

4. Clinical Data

4.1. Clinical pharmacology

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

Primary studies

No regular primary clinical pharmacodynamic studies on diuretic activity are available.

Secondary studies

Hypotensive effects

During studies on influence of aqueous corn silk extract on intraocular pressure in forty (42-54 years) randomised volunteers with two level of hypertension, 20 systemic and 20 non-systemic hypertensives George & Idu (2015) observed also influence on blood pressure. The systemic hypertensives were classified those not treated volunteers, who had systolic pressure of 140 to 160 mmHg, diastolic pressure of 90 to 105 mmHg (group A); the non-systemic hypertensives were those who had an average systolic pressure less than 140 mmHg and diastolic pressure less than 90 mmHg (group B). During the screening exercise the case history of all patients were taken. and each subject was generally examined, blood pressure and ocular examination contained the anterior and posterior segments of the eyes. The corn silk decoction was prepared of 480 g corn silk in 7 L of boiling water for 20 min. then concentrated. Its 600 ml corresponded to the 41 g of the herbal substance (520 mg/kg b. w.) and was diluted to the dosages corresponding: 5.14, 15.40, 10.28, 20.57 g of herbal substance in single dose volume 600 ml. The volunteers were administered with two-week intervals, in the two study groups, according to the scheme: Day 1 water, Day 2 5.14 g; Day 15 water; Day 16 15.40 g; Day 29 water; Day 30 10.28 g; Day 43 water; Day 44 20.57 g. Blood pressure was measured three consecutive times during the screening exercise, namely, at 9 am, 3 pm and 6 pm. Intraocular pressure and blood pressure were measured at baseline and every hour for eight hours after administering water or a corn silk aqueous extract. The effect of the single dose 5.14 g (60 mg/kg) decoction was significant (MANOVA test) in "not systemic hypertensives" but not in systemic hypertensive patients. Effect of dosage 10.28 g (130 mg/kg) was significant in non-systemic hypertension -8.32% lowering and -5.53 % in systemic hypertension subjects; doses 15.40 g (192.5 mg/kg) and 20.57 g (260 mg/kg) gave also significant lowering of blood pressures, stronger in mild hypertension (-13.55 and -18.36%) than more advanced hypertensions (-8.26% and -13.64%).

Assessor's comment:

The trial was not designed to study diuretic or antihypertensive activity of the extract, the data on blood pressure in volunteers have a value of pilot study. The corn silk concentrated decoction doses administered in the trial were higher than currently used in the EU countries They correspond to 5 to 20 g of corn silk, which partially overlaps the range of doses traditionally used in Britain (8-12 g) and in Poland in the fifties and sixties (7-9 g up to 30 g daily).

Hypoglycaemic effects

Haldar et al. (2019) measured postprandial glycaemic and insulinemic effects of the aqueous corn silk extract taken by 18 healthy volunteers from University of Singapore with high glycaemic index rise (Chinese, male, age 21-60 years, BMI 18.5-25.0 kg/m2, waist circumference ≤90 cm, fasting blood glucose < 7.0 mmol/L). At the screening visit weight and body fat percentage, blood pressure, fasting

glucose were measured. Corn silk decoction was prepared of 552g in 2.3 L, boiled for 15 min. 50 ml of concentrated extract (24g/100ml) and diluted to the volume of 200 ml before use to obtain "diluted aqueous extract". The extracts were added into rice of the study meals every morning or made up into drink. Every volunteer came for five or nine sessions with a minimum 1-day wash-out between. The order of the study meals was randomised with Rand function in MS Excel. Upon arrival, volunteers had their baseline (T0) blood pressure measured and a fasted blood sample drawn (after 5 min of rest), then served the study meal and instructed to consume it within 15 min. Subsequent blood collection was carried out at 15, 30, 45, 60, 90, 120, 150, and 180 min. after the first bite. Blood pressure measurements were taken hourly at 60, 120, and 180 min. The study in healthy volunteers not confirmed additional benefits on postprandial glycemia or insulinemia.

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

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

Not data available

4.2.2. Clinical studies (case studies and clinical trials)

Clinical trials

There are no available clinical trials on single-component medicines with corn silk preparations used for the relief of symptoms associated with minor urinary tract complaints.

Shi et al. (2019) reviewed results of trials where corn silk tea was used in patients with hypertension, to try to assess possible improvement of their clinical outcomes. The review included 5 trials, which were available until 2018. 5 randomized controlled (567 patients) were included. The main outcome was total blood pressure lowering efficacy. To assess methodological quality of the trials Cochrane Handbook was used. For data analyses was used Review Manager 5.3 software. Due to the methodological quality, only limited evidence showed that the corn silk tea, plus antihypertensive drugs, might be more effective in lowering blood pressure compared to the antihypertensive drugs alone. Also, there was no evidence that the tea plus antihypertensive drugs have less adverse events.

4.3. Clinical studies in special populations (e.g. elderly and children)

Clinical studies are not available.

Case report

Kruesi (2016) reported on 9-year-old girl who had primary nocturnal enuresis since birth, with no known dry nights since birth but without daytime enuresis or urine leakage during a day. The disease was unresponsible to multiple trials of pharmacotherapy, with evidence for supporting their use of imipramine up to 2 mg/kg for 6 weeks, desmopressin in doses 40 µg as nasal spray and 0.4 mg orally plus atomoxetine. Although all the pharmacology had failed in gaining even a single dry night. The

father of the patient reported that he also had nocturnal enuresis through adolescence but stated that his Native American grandmother had brewed a decoction using a quart plus one tablespoon of water (ca. 960 ml) plus the green part of the silk from a dozen ears of fresh corn (20-30g?), which was brought to boil, allowed cool, strained and used with a first dose a cup full on the first night and then a tablespoon dose each night until the decoction was gone. After the girl's enuresis had failed to be cured with the prescription medicines, she and her mother decided to try to use the corn silk tea treatment. The patient experienced full remission after completion the same treatment, without wet nights. The author stated that he knew that also hydrochlorothiazide was reported to be better than placebo for nocturnal enuresis or improving enuresis but in the absence of pharmacologic trials he was not sure whether it was any kind of specific placebo effect.

Assessor's comment:

The use of corn silk by herbalists in curing nocturnal enuresis was known by urologists in America; it was mentioned by Culbert and Banez (2008) in their review on treatment of enuresis in paediatric patients and described by Kruesi (2016).

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no available well designed clinical trials on diuretic activity of corn silk water extracts. The current requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC as amended is considered not fulfilled.

5. Clinical Safety/Pharmacovigilance

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

No data available from clinical trials in humans

5.2. Patient exposure

No data available on number of corn silk tea users in Europe.

Table 8: Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
5 reviewed randomized controlled trials (placebo-controlled + active–controlled), Shi (2019)	567	No data	No data	Not available
Open studies, George & Idu (2015),	58	58	No data	Not available
Case reports, Kruesi (2016)	1	1		

* In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment:

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

There are no reports on Corn Silk from EudraVigilance nor available national databases.

There is one report from India (Vigibase), where one male patient (age 45-64), suffered with myositis, reported to take corn silk preparation together with other medicines and food supplements (insulin, fenofibrate, rosuvastatin, *Paulinia cupana* preparation, and vitamins) and. As myositis aetiology is not known and some scientists incline to genetic predisposition theory, with possible environmental triggering factor, cause relationship between the myositis and use of corn silk product is unsure.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

The use in children under 12 years of age has not been established due to lack of adequate data.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

To ensure an increase of the amount of urine, adequate fluid intake is required during treatment.

The use in children under 12 years of age has not been established due to lack of adequate data.

If urinary tract complaints worsen and symptoms such as fever, dysuria, spasm, or blood in the urine occur during the first week of use of medicinal product, a doctor or a qualified health care practitioner should be consulted immediately.

Because adequate fluid intake is required during treatment (see section 4.2. Posology and method of administration), *Zea mays* stigma (silk corn) is not recommended for patients with conditions where reduced fluid intake is advised by a medical doctor.

5.5.4. Drug interactions and other forms of interaction

None reported.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

5.5.8. Safety in other special situations

No data.

5.6. Overall conclusions on clinical safety

There are no available clinical safety trials.

6. Overall conclusions

Well established use monograph

The current requirements for well-established medicinal use according to Article 10a of Directive 2001/83/EC as amended is considered not fulfilled because of lack of clinical data on recognized efficacy.

Traditional use monograph

According to the market overview and literature data, the following preparation fulfils the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use according to Directive 2004/24/EC. The preparation has been used in specified posology of half to two tablespoons (2 to 8 g) of the comminuted herbal substance for a glass of water for decoction, used 2-3 times daily, without the need of medical consultation. The traditional use was plausible on the base of the available data.

The herbal substance does not contain any constituents known for safety concerns.

The preparation has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use according to Directive 2004/24/EC for one herbal preparation: herbal tea, decoction used in the indication:

Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC. Typical analytical marker was not established.

The requirements for traditional medicinal use according to Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC are considered fulfilled. It has been demonstrated that *Zea mays* L., stigma has been in traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, with an acceptable level of safety for:

Herbal substance/ preparation	Indication	Therapeutic area for browse search	Posology and method of administration	Duration of use
Zea mays L., stigma/Herbal tea, decoction.	Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine	Urinary tract and genital disorders	Adolescents, adults and elderly: Herbal tea, decoction, of 2–4 g of the herbal substance in 200 ml of water (boiled for 5 minutes). Drink the of the fresh prepared, strained decoction, 2-3 times daily, between meals. Daily doses: 4 - 12g. Adolescents, adults and elderly: Herbal tea, infusion of 4– 8 g of comminuted herbal substance in 200 ml of boiling water 3 times daily Daily doses 12 g – 24.0 g	Two weeks without medical consultation

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

One test on genotoxicity has been performed with the ethanol fraction of the water extract of *Zea mays* L., stigma, which was obtained of the herbal substance, but these data cannot be extrapolated to herbal tea proposed in the MO. Therefore, a European Union list entry cannot be supported.

Annex

List of references