ThemenCheck Medizin

Extract of HTA report

Bladder infection[1]

Do herbal remedies help with recurrent bladder infection?

Health technology assessment commissioned by IQWiG

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IQWiG coordinated the project, conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”, and prepared the easily understandable summary “HTA compact”.

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A12 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The assessment is done in the form of a Health Technology Assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics are supposed to be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In the year 2020, IQWiG commissioned a team of scientists led by the Austrian National Public Health Institute (GÖG) to investigate the selected topic of "Bladder infection: Are herbal remedies effective against recurrent uncomplicated bladder infection?". The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as a urologist.

Why is the HTA report important?

In uncomplicated bladder infection (cystitis), the mucosa of the urinary bladder becomes inflamed. This inflammation is typically caused by bacteria which travel through the urethra into the bladder, where they multiply. Bladder infection is much more common in women than in men. Typical symptoms are a painful, frequent, or uncontrollable urge to urinate, pain when urinating, and pain above the pubic bone. Recurrent bladder infection is defined as 2 or more symptomatic episodes within a half year or 3 or more episodes within a year. According to a drug report issued by Barmer health insurance, about 9% of female insured persons had bladder infections in 2013 [2]. In a British representative survey study including 2424 women from Great Britain aged 16 years and older, about 3% reported having had 3 or more urinary tract infections in the prior 12 months [3].

Treatment options for (recurrent) bladder infection comprise both antibiotic and non-antibiotic therapies. In acute bladder infection, antibiotics typically take effect fairly quickly and shorten the disease duration. But they are not always necessary. Thirty to 50 out of

100 women recover from uncomplicated bladder infection within a week, even without antibiotics [4].

Non-antibiotic therapies for treating acute bladder infection or preventing recurrence include various herbal preparations (phytopreparations). They comprise extracts from a wide range of different plants (or plant components), e.g. cranberry, uva ursi leaves, nasturtium herb, or horseradish root. These substances are reported to have antimicrobial, anti-inflammatory, or diuretic effects and thereby reduce the duration of acute bladder infections or prevent their recurrence.

In the topic proposal for this HTA report, the suggesting party notes that many people are critical of the frequent use of antibiotics. However, according to the suggesting party, antibiotics are typically recommended for treating bladder infection. The suggesting party therefore asks whether alternatives to antibiotic treatment in the form of herbal preparations exist for women with uncomplicated recurrent bladder infection, both for treating acute bladder infection and for preventing recurrences.

To answer the suggesting party's question, the commissioned team of authors looked at the different perspectives of an HTA report and investigated whether women with recurrent bladder infection benefit from treatment with herbal preparations. A benefit exists if studies show that herbal preparations contribute to women with recurrent bladder infections contracting bladder infections less frequently. This would also be true if said women benefit from herbal preparations during the treatment of an acute bladder infection, e.g. by reducing the painful or frequent urge to urinate.

Which questions are answered – and which are not?

For assessing the benefit and harm of herbal preparations, the team of scientists led by the GÖG included 15 studies which investigated a total of 9 different plant components. A total of 12 studies investigated preparations containing at least cranberry as an active component; 8 of these 12 studies compared cranberry preparations versus placebo, 2 versus antibiotics, 1 versus different herbal medicinal products, and 1 study investigated cranberry preparations in different dosages. The 3 remaining studies investigated other herbal preparations, e.g. uva ursi leaves and dandelion or lovage root, rosemary leaves, and common centaury herb, 2 of them in comparison with placebo, and 1 as an add-on to antibiotics.

The experts found an indication of benefit for cranberry when compared to placebo with regard to a lower recurrence rate. For the prevention of recurrence, for instance, the metaanalysis in which the commissioned group of authors combined the results of 6 studies shows a statistically significant advantage of cranberry preparations versus placebo (IRR = 0.58; 95% CI = [0.38; 0.89]; n = 1151) over a period of typically 6 to 12 months. The

authors additionally derived from the studies a hint regarding an extension of the recurrence interval.

A comparison of cranberry preparations versus antibiotic long-term treatment, both for recurrence prevention, reveals a hint of lesser benefit of cranberry preparations. Antibiotics for recurrence prevention in the form of antibiotic long-term therapy is not the treatment of first choice; the S3 guideline on bladder infections [4] recommends it for a period of 3 to 6 months, but not until after other measures such as behavioural changes and non-antibiotic prevention measures have failed as well as in patients experiencing a high level of suffering.

The commissioned authors also found studies investigating herbal remedies other than cranberry. For recurrence prevention, they report, e.g. hints of benefit for a preparation made of uva ursi leaves and dandelion compared to placebo as well as hints of added benefit (in combination with antibiotics) of a preparation made of lovage root, rosemary leaves, and common centaury herb compared to antibiotic monotherapy.

The authors of the HTA report deemed the risk of bias across outcomes to be high for most studies. Notably, only 1 of the included studies reported results on health-related quality of life (finding no significant differences between the intervention and comparator groups). Further, the reporting of adverse events by the included studies differs in the level of detail provided and is inadequate in some cases.

The authors of the HTA report also point out that the investigated cranberry preparations differ in composition. Eight studies investigated monopreparations, 3 studies examined combination preparations, and 1 study compared 1 combination preparation versus 1 monopreparation. Since insufficient information was available on the production of the preparations, definitive statements on potency were not possible in some cases. The HTA report's authors therefore note that it remains unclear whether the reported study results are transferable to all available preparations containing cranberry.

The HTA report investigates 2 questions: (1) whether herbal preparations help women with recurrent bladder infection avoid future bladder infections and (2) whether said women benefit from herbal preparations during the treatment of an acute bladder infection. The results presented by the authors of this HTA report relate almost exclusively to the first question, i.e. regarding the prevention of bladder infection. It was impossible to answer the HTA report's second question regarding the benefit of herbal preparations during acute bladder infections for women with recurrent bladder infections.

In Germany, the costs of herbal preparations are typically not (fully) covered by statutory health insurance. For an assumed 6-month treatment period, patients who use herbal preparations for preventative purposes incur costs for herbal preparations of €60 to €320.

Due to marked deficiencies in quality and transparency as well as a lack of transferability to the German healthcare context, the results of the studies investigating the cost effectiveness of herbal preparations were unusable for assessing cost effectiveness. Therefore, no conclusion can be drawn on cost effectiveness.

Preparations made from the investigated plants or plant components are marketed as either herbal medicinal products or dietary supplements and are sold in various pharmaceutical forms, such as capsules, tablets, and powders as well as teas and juices. Often, the preparations' active ingredient content is not clearly specified. Patients are therefore confronted with a very intransparent market of herbal medicinal products and dietary supplements.

From an IQWiG perspective, this HTA report comprehensively summarizes results regarding the benefit of herbal preparations in the prevention and treatment of recurrent bladder infection. Despite limitations owing to the studies' typically high risk of bias, limited data provided on adverse events, and inadequate description of active ingredients, the report shows that cranberry preparations, in particular, can play a role in recurrence prevention in women with uncomplicated recurrent bladder infections. It would be a welcome development if the use of certain herbal preparations were to lead to reduced antibiotics use – both for treating and preventing acute bladder infection – and thereby contribute to reduced antibiotic resistance. However, it should be noted that no data are available on the use of herbal preparations in the acute treatment of symptomatic episodes in women with recurrent bladder infections.

What's the next step?

The herbal preparations used in the studies appear to generally correspond to common preparations available in Germany. However, the interpretation of study results is complicated by the fact that studies often provide imprecise information on the dosages of cranberry preparations and that particularly the herbal combination preparations investigated in the studies do not exactly match products commercially available in Germany. It would be helpful for future studies, e.g. those on cranberry preparations, to consistently provide information on the content of proanthocyanidins (PAC), which, based on microbiological studies, are believed to cause the potential effects of cranberry. This information might also help patients maintain an overview of the complex market of herbal medicinal products and dietary supplements.

This HTA report found an indication of cranberry preparations reducing the recurrence rate and a hint of them extending the interval until the next recurrence compared with placebo. Since 2017, the S3 guideline for bladder infection has also included recommendations on non-antibiotic recurrence prophylaxis, but only for D-mannose and herbal urinary antiseptics (uva

ursi leaves, nasturtium herb, horseradish root). According to the S3 guideline, it was impossible to issue a recommendation for the prophylactic use of cranberry products due to contradictory study results [4]. This was also noted in 1 comment on the preliminary HTA report. The HTA report's authors argue that their conclusion deviates from the S3 guideline in part due to study results which had not yet been available at the time the S3 guideline was written: A total of 6 of the studies included in this HTA report were published after publication of the S3 guideline. These study results should therefore be taken into account in the currently ongoing update of the S3 guideline.

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HTA key statements

Research question of the HTA report

The aims of this investigation are to

- assess the benefit of treatment with herbal remedies (phytopreparations) in comparison with different or no treatment in adult patients (16 years and older) with uncomplicated, recurrent lower urinary tract infections (UTIs) regarding patient-relevant outcomes,

- determine the costs (intervention costs) and assess the cost effectiveness of phytopreparations in comparison with different or no treatment in adult patients (16 years and older) with uncomplicated recurrent lower UTIs and

- review ethical, social, legal, and organizational aspects associated with the medical intervention.

Conclusion of the HTA report

The benefit of phytopreparations in comparison with different or no treatment in adult women with uncomplicated recurrent lower UTIs was investigated by 15 studies meeting this health technology assessment (HTA) report's inclusion criteria. Among the 34 plants (or part components) which had been predefined as being relevant for this HTA report, 9 were investigated in the included studies.

Most studies examined preparations containing cranberry. This results in an indication of benefit for cranberry in comparison with placebo regarding the reduction of recurrence rate and a hint regarding the extension of the interval until the first recurrence. There is a hint of lesser benefit of cranberry regarding recurrence prevention when compared with antibiotics, specifically trimethoprim sulphamethoxazole. Aside from cranberry, isolated study results are available on preparations containing the following plants (or plant components): 1 preparation with horseradish root and nasturtium herb, 1 preparation with uva ursi leaves and birch, 1 preparation with uva ursi leaves and dandelion, and 1 preparation with lovage root, rosemary leaves, and common centaury herb. The assessment found a hint of benefit for a preparation made from uva ursi leaves and dandelion in comparison with placebo as well as a hint of added benefit (in combination with antibiotics) of a preparation made of lovage root, rosemary leaves, and common centaury herb versus antibiotic monotherapy for recurrence prevention. Very few data are available for the outcomes of health-related quality of life, development of complicated infections, specific symptoms, and mortality. For mortality and health-related quality of life, this results in no hint of benefit for cranberry preparations

in comparison with placebo. For specific symptoms, there is no hint of benefit for a preparation made of lovage root, rosemary leaves, and common centaury herb in combination with antibiotics when compared with antibiotic monotherapy. No further conclusions on benefit can be drawn regarding these outcomes.

No adverse events data are available for comparing a preparation made of lovage root, rosemary leaves, and common centaury herb in combination with antibiotics versus antibiotic monotherapy; no conclusion can be drawn on benefit. For all other comparisons investigated herein, the reported adverse events show no hint of greater or lesser harm from one of the investigated preparations in comparison with the respective comparator intervention.

The transferability of the benefit assessment's results to Germany is limited by the fact that not all herbal preparations investigated in the benefit assessment correspond to commercial products available in Germany. More than half of the cranberry monopreparations and 2 of the preparations without cranberry (uva ursi leaves and birch as well as uva ursi leaves and dandelion) were either impossible to find, inadequately described, or no longer (if ever) available on the market.

With regard to the determination of costs, the available studies and data placed the focus on long-term prevention. Among the investigated phytopreparations, the cost of 6 months of treatment with these foods or dietary supplements ranged from €60 to €270; these costs must be borne by the patients out of pocket. For other herbal medicinal products which were classified as pharmaceuticals by the LAUER-TAXE® pharmaceuticals database, costs equalled €110 to €300; some of these costs were covered by health insurance companies on a case-by-case basis. For "general preventive measures and non-antibiotic therapies" which, according to the S3 guideline, are to be exhausted before potentially initiating long-term preventive antibiotic treatment, prevention with phytopreparations therefore incurs potential semiannual costs to be paid by patients in the two-digit to low three-digit range. For 6 months of long-term preventive therapy with antibiotics, in contrast, patients incurred costs of (a maximum of) about €20 to €35 (at total costs of up to €130).

According to cost effectiveness literature on cranberry prophylaxis (compared with placebo), the enhanced effectiveness with respect to recurrence prevention is juxtaposed by higher direct costs. Cranberry's lower effectiveness in recurrence prevention when compared with antibiotic prevention is paired with higher cost (than antibiotics), making cranberry prophylaxis the predominant alternative over antibiotics. However, this calculation ignored the potential costs of antibiotic resistance. Due to poor transferability and substantial deficiencies in quality and transparency, however, the identified health economic evaluations are of very limited use for assessing cost effectiveness in the present HTA report. In any case, important factors influencing the cost effectiveness of cranberry prophylaxis in comparison with antibiotic prophylaxis were found to be effectiveness in recurrence prevention (and the

associated cost savings), the cost of the preparations themselves, and potential cost savings achieved by preventing antibiotic resistance.

The legal situation is complex because preparations made from the investigated plants (or plant components) may be marketed as either herbal medicinal products or dietary supplements. Unlike prescription drugs, dietary supplements do not require proof of efficacy, while herbal medicinal products do so only to a limited extent. For patients, very similar packaging often additionally complicates determining a preparation's product category. Herbal medicinal products are reimbursed by health insurance funds only in isolated cases, and dietary supplements are never reimbursed. This aspect is relevant from an ethical and social perspective because many patients would like to use herbal medicinal products to treat lower UTIs, but they have to pay for them out of pocket. For society, potentially reducing antibiotic use via herbal medicinal products is a highly relevant aspect. Since current guidelines recommend antibiotics for the long-term prevention of lower UTIs only in exceptional cases, said societal aspect primarily concerns the acute treatment of lower UTIs. However, no study data are available on the efficacy of herbal medicinal products in the acute care of lower UTIs in women with recurrent uncomplicated lower UTIs.

Further research is needed: High-quality studies providing detailed information on the investigated preparations' composition would allow making more definitive statements regarding the effectiveness and transferability of these conclusions to preparations available in Germany. If appropriately disseminated, this information might help affected patients navigate through the very nontransparent market of herbal medicinal products and dietary supplements. Studies proving effectiveness are also a prerequisite for approval as prescription-only drugs and hence for general reimbursability. This approval, in turn, would give all affected patients easy access to (effective) PPs.

Two currently ongoing studies (which both investigate cranberry preparations) might supply additional data relevant for the research question.

Conclusion in terms of addressing the concerns of those proposing the topic:

The preventive use of cranberry preparations may be a good option for women with uncomplicated recurrent lower UTIs because such use is associated with an indication of benefit for relapse prevention in comparison with placebo, and the S3 guideline recommends preventive use of antibiotics only in exceptional cases. Due to very limited data being available, it is impossible to assess whether the preventive use of other phytopreparations may be a good option. No data are available on the use of cranberry preparations or other phytopreparations in the acute treatment of symptomatic episodes experienced by women with uncomplicated recurrent lower UTIs.

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List of abbreviations

Abbreviation	Meaning
AMG	Arzneimittelgesetz (Medicinal Products Act)
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
CI	confidence interval
EMA	European Medicines Agency
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
HTA	health technology assessment
IC	interstitial cystitis
IRR	incidence rate ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NemV	Nahrungsergänzungsmittelverordnung (German Food Supplements Ordinance)
PAC	proanthocyanidin
PBS	painful bladder syndrome
PP	phytopreparations
QALY	quality-adjusted life years
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
SGB	Sozialgesetzbuch (German Social Code Book)
SHI	statutory health insurance
SPC	Summary of Product Characteristics
TMP	trimethoprim
TMP-SMX	trimethoprim sulphamethoxazole
UTI	urinary tract infection

HTA overview

1 Background

1.1 Health policy background and commission

According to § 139b (5) of Social Code Book V, Statutory Health Insurance, statutory health insurance members and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the IQWiG ThemenCheck Medizin website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about healthcare services and structures. The HTA report will be made available to the professional community through the IQWiG website (www.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

The term "bladder infection" is used in common parlance; from a medical perspective, this disorder represents an inflammation of the lower urinary tract (bladder and urethra), which is lined by typically uniformly inflamed, continuous mucosa (urothelium). This HTA report therefore uses the term "lower urinary tract infection" (lower UTI), while the title and the "HTA compact" format continue to refer to the condition as "bladder infection". The information on medical background presented below is predominantly based on the S3 guideline issued by the German Society of Urology, AWMF registry number 043/044 [1].

1.2.1 Clinical picture

Typical symptoms of lower UTI include a painful, frequent, or imperative (uncontrollable) urge to urinate, pain during urination, and suprapubic pain (pain above the pubic bone). Fever (> 38°C), flank pain, and pain elicited by percussion in the kidney area are signs of the

inflammation ascending to the ureter and renal pelvis (upper urinary tract infection [UTI] – pyelonephritis) [2]. Uncomplicated lower UTIs are often self-limiting. Severe courses of disease are promoted by a series of complicating factors, e.g. anatomic and functional disorders of the urinary tract, pregnancy, renal dysfunction, and other diseases which facilitate UTIs. These include kidney stones, hepatic impairment, a suppressed immune system, chemotherapy, radiotherapy, urinary catheters, etc. In men, UTIs are generally deemed complicated [1]. Some individuals repeatedly develop lower UTIs. Recurrent UTI is defined as 2 or more symptomatic episodes occurring within a half year or 3 or more episodes within a year.

1.2.2 Aetiology, diagnostics, and prognosis

(Recurrent) UTIs often result from bacterial infections, which typically develop as the result of microbes ascending (germs moving upward) from the faecal reservoir. Virtually all of these infections are monoinfections by a single bacterial strain. While several different bacterial strains can be the cause of (recurrent) UTIs, *Escherichia coli* is by far the most common one, being identified in over 75% of patients [3,4].

The diagnosis of (recurrent) UTIs always requires clinical symptoms. Since even the urine of asymptomatic patients often contains bacteria, neither a positive dipstick test nor positive urine culture suffice, in isolation, for diagnosing (recurrent) UTI. The diagnosis of (recurrent) UTI is established on the basis of the patient's medical history and testing for bacterial infection, but both false-positive and false-negative findings are common [5]. Vaginal complaints such as itching or discharge are relevant for differential diagnostics. In their presence, gynaecological examinations and alternative diagnoses should be taken into consideration. In women who experience recurrent UTIs and exhibit suspected complicating factors, e.g. urinary stones, sonography should be additionally performed [1]. In clinical practice, rapid tests are often used for detecting bacterial infection; these tests confirm infection indirectly by measuring nitrite levels and/or leukocyte (white blood cell) counts in urine. Compared with the gold standard – direct confirmation of infection by growing bacteria in a urine culture – these rapid tests are less specific and less sensitive and can therefore lead to overdiagnosing and underdiagnosing infections [6]. Furthermore, urine samples examined in clinical practice are often collected midstream rather than under sterile conditions; this may lead to false-positive bacterial cultures due to contamination by vaginal flora [1].

In patients without bacterial infection, (recurrent) UTIs may be caused by damage to the urothelium. If perturbed in its physiological function, the urothelium becomes permeable. As a result, potassium, which is highly concentrated in urine, can flow into the muscle tissue below the urothelium and cause other symptoms [7]. Dysfunctional urothelium may additionally facilitate bacterial infection, and patients may exhibit both simultaneously. Interstitial cystitis (IC or PBS, painful bladder syndrome) should be taken into account in terms

of differential diagnostics. IC/PBS is a noninfectious chronic bladder disease; it represents a separate disorder with varied symptoms and is of unclear aetiology [8].

Lower UTIs or individual symptomatic episodes of recurrent UTIs are associated with a high spontaneous recovery rate, but recovery can be sped up by therapeutic interventions [9–11]. Bacterial UTIs which resolve slowly or not at all are associated with a risk of symptoms worsening and kidney inflammation (pyelonephritis) developing [11].

1.2.3 Epidemiology and risk factors

UTIs are far more common in women than in men, in part for anatomic reasons such as a shorter urethra and smaller distance between the genital and anal regions. Further UTI-promoting factors are higher age (postmenopause), sex, and certain contraceptive methods (e.g. diaphragms or spermicidal agents) [1,12]. During menopause, hormonal changes also alter the vaginal flora which is then colonized by more bacterial strains capable of causing UTIs [12].

The incidence of (recurrent) UTIs cannot be precisely determined, because not all people contracting them consult a physician. The most recent data available for Germany are from the Barmer GEK's Pharmaceutical Report. The diagnosis of "urinary tract infection" or "acute cystitis" was established in 8.68% of female insured persons in 2012 and in 9.05% in 2013, with an additional 0.16% being diagnosed with "pyelonephritis" (in 2012 and 2013) [13]. In 2015, a representative survey was conducted in Great Britain among 2424 women over 16 years of age. In this survey, 37% of participants reported having experienced a UTI at some point in their lives, and 11% indicated having had a UTI within the prior year [14]. In addition, 3% of participants reported 3 or more UTIs in the past year (recurrent UTI).

1.2.4 Treatment

Treatment options for (recurrent) lower UTIs comprise both antibiotic and non-antibiotic therapies. In the absence of complicating factors, the use of antibiotics is not always necessary. Treatment should be selected in consideration of individual patient preferences [1]. In the treatment of recurrent lower UTIs, treatment goals are (a) symptom alleviation during the current episode and (b) reduction of the recurrence rate.

1.2.4.1 Antibiotic treatment of (recurrent) lower UTIs

Generally, several suitable antibiotics or antibiotic classes are available for treating (recurrent) lower UTIs: aminopenicillins in combination with a beta-lactamase inhibitor, group 2 or 3 cephalosporins, fluoroquinolones, fosfomycin-trometamol, nitrofurantoin, nitroxoline, pivmecillinam, trimethoprim, and cotrimoxazole [1]. In patients with uncomplicated lower UTIs, antibiotics are typically used empirically, while identifying the pathogen is recommended in complicated lower UTIs and recurrent lower UTIs. In any case, the regional pathogen

spectrum and regional resistance development must be taken into account [1]. In general, caution must be exercised when using antibiotics because their use may result in (a) the increased development of resistant strains and (b) *Clostridium difficile* infections because of an altered intestinal flora. The principles of responsible antibiotics use (antibiotic stewardship, ABS) must be observed [15]. For this reason, fluoroquinolones and cephalosporins are not recommended as first-line therapy in uncomplicated (recurrent) lower UTIs. Furthermore, short-term therapy (1 to 3 days) rather than conventional antibiotic therapy (7 to 10 days) is recommended as standard treatment [1]. This recommendation is based in part on a metaanalysis which found no differences in effectiveness between short-term therapy and conventional therapy but more side effects for conventional therapy [16]. Antibiotics and antibiotic classes differ markedly in their potential adverse drug effects, but many antibiotics can lead to gastrointestinal disorders or allergic reactions.

1.2.4.2 Phytopreparations for the treatment of (recurrent) lower UTIs

As alternatives to antibiotic therapy, various herbal remedies (phytopreparations, PPs) can be used to treat (recurrent) lower UTIs. They comprise extracts in various pharmaceutical forms, e.g. capsules, tablets, and powders as well as teas and juices. The various available PPs are produced from a wide range of different plants (or plant components). For this HTA report, a list of plants (or plant components) relevant for the treatment of (recurrent) lower UTIs was generated based on the S3 guideline issued by the German Society of Urology [1] and the "EU Herbal Monograph" Registry published by the European Medicines Agency (EMA) (entries for the therapeutic indication "urinary tract disorders"; last visited 20 October 2020) [17]. The EMA registry lists plants (and plant components) whose therapeutic efficacy has either been demonstrated by clinical study data or is plausible based on long-standing traditional use. The list was further supplemented by a urologist as well as a pharmacist working in Germany, who added 3 plants (turmeric, smallflower hairy willowherb, silverweed) which are used in practice for treating uncomplicated lower UTIs (see Table 1).

Table 1: List of plants (and plant components) from which PPs are produced for treating (recurrent) lower UTIs

Uva ursi leaves	Turmeric
Birch leaves	White cedar tips, leaves
Stinging nettle herb, leaves	Lovage root
Rupture wort	Dandelion leaves, root, herb
Watercress herb	Mate leaves
Cranberry	Horseradish root
Strawberry leaves	Orthosiphon leaves
Ash leaves	Parsley herb, root

Common bean pods	Echinacea root
Silverweed	Couch grass rhizome
Goldenrod herb	Rosemary leaves
Hawkweed herb, root	Horsetail herb
Restharrow root	Black currant leaves
Indigo root	Common centaury herb
Chestnut bark	Knotweed herb
Smallflower hairy willowherb	Juniper berries and essential oil
Burdock root	White sandalwood
PP: phytopreparation; lower UTI: urinary tract infection	

The general mode of action of PPs is difficult to explain because many different plants (and plant parts) with different potentially effective ingredients are used in the treatment of (recurrent) lower UTIs. Potential mechanisms of action of various ingredients include, e.g. bacteriostatic, anti-inflammatory, or diuretic effects, inhibition of bacterial adhesion, and restoration of the urothelium's physiological milieu [1].

1.2.4.3 Other treatment options

Antibiotics and PPs can also be used in combination for the treatment of (recurrent) lower UTIs. In recurrent lower UTIs, certain behavioural modifications, e.g. with regard to hygiene, sexual behaviours, or drinking habits may also contribute to reducing the recurrence rate. Furthermore, a series of products for stimulating the immune system are available for preventive purposes (inactivated microbes or parts thereof; various application methods). Further treatment options comprise anti-inflammatory agents, certain sugars (glycosaminoglycans, mannose), chemical urinary tract antiseptics, long-term antibiotic therapy for prophylaxis, and acupuncture [1].

1.3 Health care situation

PPs are found in both drugs and foods (e.g. dietary supplements). The latter require no approval (e.g. in Germany and Austria) and consequently no specification of a therapeutic indication. Dietary supplements are neither prescription-only nor pharmacy-only products and can be purchased in pharmacies, drugstores, online, etc. While most herbal medicinal products are pharmacy-only, they likewise do not require prescriptions. Unlike for prescription drugs, no verifiable conclusions can therefore be drawn on the use of PPs in the treatment of (recurrent) lower UTIs [13]. As per Section 34 of the German Social Code Book V (SGB V), with few exceptions, non-prescription drugs cannot be prescribed through the statutory health insurance (SHI). Therefore, the cost of PPs is typically paid by patients out of

pocket. According to the German SHI Health Care Structure Act (GKV-VStG), however, health insurance funds are free to include non-prescription drugs in their optional benefits up to a certain amount. This benefit requires a physician to recommend a specific non-prescription drug on a “green prescription”.

Among the insured members of Barmer GEK, female patients with the diagnosis “lower UTI” or “acute cystitis” were prescribed antibiotics in 57% of cases (in the year 2012) and 60% (in 2013) [13]. In a British survey, 74% of women who had consulted a physician for lower UTIs reported being prescribed antibiotics. However, only 63% of these women reported actually taking the antibiotics [14].

1.4 Concerns of those proposing the topic

Regular use of antibiotics is viewed critically by many people. According to the suggesting party, however, the use of antibiotics is typically recommended for uncomplicated lower UTIs. The suggesting party is therefore interested to find out whether an alternative to antibiotic treatment exists for women with uncomplicated lower UTIs.

2 Research questions

The aims of this investigation are to

- assess the benefit of treatment with phytopreparations in comparison with different or no treatment in adult patients (16 years and older) with uncomplicated, recurrent lower UTIs regarding patient-relevant outcomes,
- determine the costs (intervention costs) and assess the cost effectiveness of phytopreparations in comparison with different or no treatment in adult patients (16 years and older) with uncomplicated recurrent lower UTIs and
- review ethical, social, legal, and organizational aspects associated with the medical intervention.

3 Methods

This HTA Report has been generated based on the *General Methods 6.0* [18].

3.1 Methods – benefit assessment

The target population of the benefit assessment is patients ≥ 16 years with recurrent UTIs. The investigational intervention is treatment with PPs (monotherapy or as an add-on to any other therapy) containing one or more of the plants (or plant parts) listed in Table 1. No limitations were applied to the comparator intervention.

The following patient-relevant outcomes were taken into account in the assessment:

- Morbidity, e.g.
  - specific symptoms (e.g. painful, frequent, or uncontrollable urge to urinate, pain when urinating, suprapubic pain, abdominal cramps),
  - development of complicated infections (ascending infections),
  - time until next recurrence,
  - recurrence rate (frequency of subsequent recurrences)
- Health-related quality of life
- Adverse events
- Mortality

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

A systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: study registry and systematic reviews.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria for risk of bias were assessed, and the risk of bias was rated as high or low in each case in accordance with the *General Methods 6.0* [18]. The results of the individual studies were described in the order of outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met. A final summarizing evaluation of the information was carried out in any case.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: there was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Six studies with comparable research questions and data on recurrence rates were examined for heterogeneity by means of a statistical test. Since the heterogeneity test delivered a nonsignificant result, a metaanalysis was performed using the random-effects model according to the Knapp and Hartung method using the heterogeneity estimator by Paule and Mandel [19]. As an effect measure, the incidence rate ratio (IRR) was calculated [20]. The person-time needed for this purpose was calculated as follows [21]: (1) In the analysis of the operationalization "number of patients with at least 1 recurrence in the observation period" (time-to event analysis), the number of patients without recurrence was multiplied by the number of months in the entire observation period. The number of patients with recurrence was multiplied by the number of months in half the observation period. Both results were added to obtain the person-time per study arm; (2) for the analysis regarding the operationalization "number of recurrences per study arm", the number of all analysed patients was multiplied by the number of months in the entire observation period to determine person-time per study arm.

The calculation was performed using the statistics software R ("tidyverse" and "meta" packages) [22–24]. The joint effect including CI and prediction interval was presented as the result.

3.2 Methods – health economic assessment

To calculate intervention costs, the average resources required directly when performing the experimental and comparator intervention were estimated. For this purpose, the services directly associated with the intervention as well as the experimental and comparator intervention were taken into account. The relevant regulated or negotiated prices of these services were used wherever possible. Where a therapy took more than one year, the average annual cost per patient was reported. Reimbursable and non-reimbursable costs were listed separately.

The systematic overview of health economic studies included cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses in German or English.

As part of the focused information retrieval, a systematic literature search was conducted in the MEDLINE and Embase databases as well as the Health Technology Assessment Database. The following sources of information and search techniques were additionally used: systematic reviews.

The identified quotes were selected by one reviewer, with a second person doing quality assurance. Data extraction relied on standardized tables based on the criteria of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [25] and the European Network for Health Technology Assessment (EUnetHTA) HTA adaptation toolkit [26] regarding the assessment of reporting quality and transferability.

The cost effectiveness results reported in the studies and the authors' conclusions were described comparatively, particularly concerning study quality, transferability to the German healthcare system, and the use of outcomes deviating from the benefit assessment.

3.3 Methods – ethical, social, legal, and organizational aspects

For the processing of ethical, social, legal, and organizational aspects, scoping searches were done in the following information sources:

- MEDLINE
- Data from regional registries, laws, regulations, or directives
- Interest-based information sources, e.g. websites of interest groups, health insurance funds
- Manual search in Google / Google Scholar

Additionally, the following documents were checked for potential ethical, social, legal, and/or organizational arguments and aspects:

- Studies included in the benefit assessment
- Studies included in the health economic assessment
- The protocol for documenting the discussion with the surveyed affected people

Since social and ethical aspects often overlap, the scoping search was conducted jointly for these aspects. To support the quality of the ethical and social analysis, the reflective-thoughts method, i.e. reflection informed by the authors' knowledge regarding potential social arguments and aspects, was applied as an additional source of information [27].

One reviewer screened the information from all information sources found in the scoping searches or all other documents for statements on ethical, social, legal and/or organizational arguments and aspects of the technology to be investigated.

The screening for ethical aspects applying to herbal remedies for recurrent UTIs was based on the principles developed by Beauchamp and Childress [28] – taking into account the aspect of increasing antibiotic resistance. Alongside the principle-based ethics approach, ethical reflection was supplemented by selected central questions developed by Hofmann et al. to facilitate ethical reflection as part of “pragmatic HTA” [29].

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

The information retrieval identified 15 RCTs as being relevant for the research question of the benefit assessment. One planned and 2 ongoing studies were additionally found. Furthermore, 6 studies of unclear status, 2 prematurely terminated studies, and 3 completed studies without reported results were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 27 November 2021.

Table 2: Study pool for the benefit assessment

Study	**Available documents**	
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**
Albrecht 2007	Yes [30]	No
Beerepot 2011	Yes [31][a]	Yes [32][b] / no
Bruyere 2019	Yes [33]	No
Genovese 2018	Yes [34]	Yes [35][b] / no
Koradia 2019	Yes [36]	Yes [37] / no
Larsson 1993	Yes [38]	No
Maki 2016	Yes [39]	Yes [40] / no
McMurdo 2009	Yes [41]	Yes [42] / no
Occhipinti 2016[c]	Yes [43]	No
Sabadash 2017	Yes [44]	No
Salinas-Casado 2020	Yes [45]	No
Stapleton 2012	Yes [46]	Yes [47] / no
Stothers 2002	Yes [48]	No
Takahashi 2013	Yes [49]	Yes [50] / no
Vostalova 2015	Yes [51]	No

a. Sections 4.5.4 and A3.3.5 of the full report also describe the discrepant clinical results reported in the accompanying health economic study Bosmans 2014 [52].
b. The study was retrospectively registered.
c. This study did not report any usable data.

4.2 Characteristics of the studies included in the assessment

The study designs of the included RCTs are highly heterogeneous with regard to the investigated study populations, interventions, and comparator interventions as well as regarding outcome recording (definition of lower UTI and recurrence).

The mean/median ages of the included patients ranged from about 25 years (Stapleton 2012 [46]) to about 63 years (McMurdo 2009 [41]), with 2 studies failing to provide detailed information on age (Genovese 2018 [34] and Sabadash 2017 [44]). The frequency of prior episodes of acute lower UTIs ranged from about 2 (Stapleton 2012) to more than 6 (Beerepot 2011 [31] and Bruyere 2019 [33]) in the prior 12 months, with 5 studies (Albrecht 2007 [30], Genovese 2018, Larsson 1993 [38], Occhipinti 2016 [43], Salinas-Casado 2020 [45]) providing no information other than inclusion criteria. Four studies investigated only premenopausal patients (Beerepot 2011, Koradia 2019 [36], Sabadash 2017, Stapleton 2012); in Bruyere 2019, 60% of patients were postmenopausal, and in Stothers 2002 [48], about 35%. The remaining 9 studies did not provide any information on menopausal status. The presence of complicating factors was an exclusion criterion in all studies except for Beerepot 2011, where in both study arms, about 14% of patients suffered from complicated lower UTIs. However, studies differed in their selection of complicating factors (see Table 15 of the full report).

Outcome recording differed principally in the definition of lower UTIs and consequently of recurrence. While in some studies, the corresponding symptoms were sufficient for establishing the diagnosis of lower UTI, other studies additionally used various cutoffs for bacterial counts in urine as a diagnostic criterion (see Table 13 of the full report). Furthermore, the studies differed in terms of the party determining recurrences: patients, their primary care providers, or study staff. Some studies provided no definitions of recurrence at all. Further differences were found concerning the durations of interventions and of observations .

With regard to the investigated interventions, the included studies can be allocated to 2 groups as follows: 12 studies which included cranberry preparations and 3 studies which investigated only preparations consisting of different PPs. The investigated cranberry preparations varied substantially in their composition: 3 of the preparations were combination preparations containing both cranberry and other ingredients defined as active substances; 8 were monopreparations which contained various additives defined as non-active substances; 1 study compared a combination preparation versus a monopreparation. The various pharmaceutical forms comprised juices, extracts, and powder. The comparability of dosages cannot be assessed because insufficient information was available on the production of the preparations.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 14 studies; 1 study (Occhipinti 2016) reported no usable data. Table 3 presents an overview of the data available from the included studies regarding patient-relevant outcomes. Most studies reported data on the outcome of recurrence rate (13 of 15 studies) or time to recurrence (8 of 15 studies) or on both outcomes. A total of 13 studies additionally reported data on adverse events. While 2 studies reported data on specific symptoms, the data from 1 of these studies were unusable for the benefit assessment (see Section 4.5.1). Data on mortality and health-related quality of life were reported in only 1 study each. One study (Beerepot 2011) reported no data on the outcome of health-related quality of life despite its study methods specifying this survey. None of the studies reported data on the outcome of development of complicated infections.

Table 3: Matrix of patient-relevant outcomes

Study	Outcomes							
	Mortality	Morbidity						QoL
	All-cause mortality / overall survival	Specific symptoms	Time to recurrence	Recurrence rate (number of patients with ≥ 1 recurrence)	Recurrence rate (number of recurrences per study arm)	Development of complicated infections	AEs	Health-related quality of life (SF-36)
Cranberry preparations vs. placebo								
Bruyere 2019	-	-	●	-	●	-	●	●
Koradia 2019	●	-	●	●	●	-	●	-
Maki 2016	-	-	●	●	●	-	●	-
Occhipinti 2016	-	o	-	-	-	-	-	-
Stapleton 2012	-	-	●	●	-	-	●	-
Stothers 2002	-	-	-	●	-	-	●	-
Takahashi 2013	-	-	-	●	-	-	●	-
Vostalova 2015	-	-	●	●	●	-	●	-
Cb preparations vs. antibiotics								
Beerepot 2011	-	-	●	●	●	-	●	x
McMurdo 2009	-	-	●	●	-	-	●	-
Other PPs vs. placebo								
Albrecht 2007	-	-	-	-	●	-	●	-

Study	Outcomes							
	Mortality	Morbidity						QoL
	All-cause mortality / overall survival	Specific symptoms	Time to recurrence	Recurrence rate (number of patients with ≥ 1 recurrence)	Recurrence rate (number of recurrences per study arm)	Development of complicated infections	AEs	Health-related quality of life (SF-36)
Larsson 1993	-	-	-	●	-	-	●	-
Other PPs + antibiotics vs. antibiotics								
Sabadash 2017	-	●	-	●	-	-	-	-
Cb preparations vs. other PPs								
Genovese 2018	-	-	-	●	-	-	●	-
Cb preparations vs. Cb preparation								
Salinas-Casado 2020	-	-	●	●	-	-	●	-

●: Data were reported and were usable.
○: Data were reported but not usable for the benefit assessment.
x: Data were not reported despite planned data collection.
-: No data were reported (no further information). / The outcome was not surveyed.
AE: adverse events; Cb: cranberry; PP: phytopreparations; QoL: health-related quality of life

4.4 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as low for 3 studies and as high for the other 12 studies. High risk of bias was due to various reasons such as unclear descriptions of the randomization or blinding methods or nontransparent patient flows (see Table 17 of the full report). Two studies (Genovese 2018 and Sabadash 2017) were not blinded.

In the 3 studies with low risk of bias on the study level (Koradia 2019, Maki 2016, and McMurdo 2009), the risk of bias on the outcome level was likewise rated as low for all patient-relevant outcomes except the following: time to recurrence in Koradia 2019 and the outcome operationalization of gastrointestinal tolerability in Maki 2016 (see adverse events, Section 4.5.6) were deemed to be associated with a high risk of bias. In both cases, this was due to the outcome being reported but not specified in the study registry entry (see Table 18 through Table 21 of the full report).

4.5 Results on patient-relevant outcomes

Below, the results on patient-relevant outcomes are presented separately by investigated comparison. Detailed results of the metaanalyses are presented in Section A3.3 of the full report.

4.5.1 Results on specific symptoms

Data on specific symptoms were reported in 2 studies.

Cranberry preparations versus placebo

However, in 1 of these studies (Occhipinti 2016), the employed questionnaires and scales, details on the analysed symptoms, and the survey time points were inadequately reported, rendering the results unusable.

Other PPs + antibiotics versus antibiotics

Sabadash 2017 (comparison of Canephron® N + ofloxacin versus ofloxacin) reported the number of patients who suffered from 1 of 4 specific symptoms (suprapubic pain, dysuria, urinary frequency, and imperative [uncontrollable] urination), both at baseline and after the intervention period (7 days). The authors reported that, in both study arms, the number of symptomatic patients decreased over the intervention period, and there was a trend towards more pronounced reduction in the intervention arm (for details, see Table 22 of the full report). In addition, a scale-based score was calculated for each patient at the 3 measuring time points (3, 6, and 12 months after study start): the symptoms of dysuria, urinary frequency, and imperative [uncontrollable] urination were each rated using a score ranging from 0 points (no symptoms) to 4 points (very severe symptoms). The authors reported the mean scores across the entire study duration (12 months) per study arm: mean for the intervention group = 3; mean for control group = 6.

Hence, there was no hint of greater or lesser benefit of Canephron® N + ofloxacin in comparison with ofloxacin for the outcome of specific symptoms.

4.5.2 Results on the development of complicated infections

None of the included studies reported data on the development of complicated infections.

4.5.3 Results on time to recurrence

Cranberry preparations versus placebo

Five studies (Bruyere 2019, Koradia 2019, Maki 2016 [39], Stapleton 2012, Vostalova 2015 [51]) reported data on time to recurrence for the comparison of cranberry preparations versus placebo. However, no metaanalysis was performed because it was impossible to meaningfully pool the reported data (for details, see Section A3.3.4 of the full report).

Two studies reported the mean number of days (with standard deviation) until first recurrence in patients treated with cranberry preparations versus patients treated with placebo (Bruyere 2019: 69.9 ± 45.8 versus 43.3 ± 45.9; Koradia 2019: 175.3 ± 20.7 versus 79.3 ± 53.9). In both studies, the between-group differences were reportedly statistically significant. Two further studies reported the hazard ratio for recurrence in patients treated with cranberry preparations versus those treated with placebo. The differences were not statistically significant in either study (Maki 2016: HR = 0.67 [95% confidence interval {CI} = 0.43–1.05], p = 0.078; n = 83; Stapleton 2012: HR = 0.78 [95% CI = 0.43–1.42], p = 0.41; n = 50). Another study (Vostalova 2015) reported only a p-value of 0.04 for the difference between the 2 groups (cranberry preparation versus placebo), without providing further information on the effect measure or interval until recurrence. It must also be noted that the analysis for the reported p-value was adjusted for several factors, and on the basis of the missing registry entry or study protocol, it is unclear whether these adjustments were made nonselectively.

In summary, the data for the outcome of time to recurrence result in a hint of benefit for cranberry preparations in comparison with placebo.

Cranberry preparations versus antibiotics

Two studies compared time to recurrence for cranberry preparations versus antibiotics. No metaanalysis was possible, because the 2 studies used different antibiotics as comparators (trimethoprim [TMP] and trimethoprim sulphamethoxazole [TMP-SMX]).

The Beerepot 2011 study (TMP-SMX) reported a much shorter and statistically significantly different median time to recurrence for the cranberry group (122 days versus 244 days; p = 0.03; n: unclear). The McMurdo 2009 study (TMP) reported a slightly shorter median time to occurrence without a statistically significant difference for the cranberry group (84.5 days versus 91 days; p = 0.479; n = 39).

For the comparison with TMP, this results in no hint of benefit, and for the comparison with TMP-SMX, in a hint of minor benefit.

Cranberry preparation (monopreparation) versus cranberry preparation (combination preparation)

One study (Salinas-Casado 2020) compared Manosar®, a combination preparation containing cranberry PAC as well as other ingredients versus PAC monotherapy. The study reported that mean time to recurrence was longer in the Manosar® group than in the PAC group (98.6 days versus 84.6 days), but no information was provided on the statistical significance of this result.

This results in no hint of greater or lesser benefit of Manosar® in comparison with PAC for the outcome of time to recurrence.

4.5.4 Results on recurrence rate

Cranberry preparations versus placebo

In 6 studies comparing cranberry preparations versus placebo, the recurrence rate was reported using the operationalization “number of patients with at least 1 recurrence in the observation period” (Koradia 2019, Maki 2016, Stapleton 2012, Stothers 2022, Takahashi 2013 [49], and Vostalova 2013). The metaanalysis of these studies shows a statistically significant advantage of cranberry preparations in comparison with placebo for recurrence prevention (IRR = 0.58 [95% CI = 0.38–0.89]; n = 1151).

Three of these studies additionally reported the total number of recurrences per study arm across the observation period (Koradia 2019, Maki 2016, Vostalova 2015) The metaanalysis of these 3 studies likewise shows a statistically significant advantage of cranberry preparations over placebo (IRR = 0.47 [95% CI = 0.34–0.65]; n = 645).

One other study (Bruyere 2019) reported only the mean number of recurrences per patient across the observation period. Since it is unclear how many patients were included in this study’s analysis, the number of recurrences per study arm cannot be calculated from the data. Therefore, it was impossible to include this study in the metaanalyses. The mean number of recurrences within 3 months was 0.7 (SD: 1.1) in the group treated with the DUAB® combination preparation (containing cranberry extract, propolis, and zinc) versus 1.3 (SD: 1.1) in the placebo group. The between-group difference was reportedly statistically significant (p = 0.0257; n: unclear).

Based on these data, proof of benefit would typically be derived for cranberry preparations (see Section A2.1.3.6 of the full report). However, no data were reported for 6 studies found to be relevant for both this comparison and this outcome based on their registry entries (see Section A3.1.4 of the full report). This results in potential publication bias and a downgrade regarding the conclusion on benefit to an indication of benefit for cranberry preparations.

Cranberry preparations versus antibiotics

Two studies (Beerepot 2011 und McMurdo 2009) reported recurrence rate data for the comparison of cranberry preparations versus antibiotics. No metaanalysis was possible, because the 2 studies used different antibiotics as comparators (trimethoprim [TMP] and trimethoprim sulphamethoxazole [TMP-SMX]).

Regarding the operationalization “number of patients with at least 1 recurrence within the observation period”, the Beerepot 2011 study reported recurrence rates of 78.2% for the cranberry group and 71.1% for the antibiotics group. The reported between-group difference was statistically significant (p = 0.03; n = 199). Additionally, for the operationalization “number of recurrences per study arm within the observation period”, a statistically

significantly larger mean number of recurrences per patient in the cranberry group was reported within the treatment period of 12 months (4 [95% CI: 2.3; 5.6] versus 1.8 [95% CI: 0.8; 2.7]; p =0.02; n = 199) and in the 3 months after treatment (0.7 [95% CI: 0.4; 0.9] versus 0.5 [95% CI: 0.3; 0.7]; p = 0.03; n = 135). In a later publication (Bosmans 2014), the authors reported deviating results for the mean number of recurrences per patient (4.3 [SE = 0.84] versus 2.7 [SE = 0.5]; mean difference: 1.6 [95% CI: -0.23; 3.5]). The deviating results were reportedly due to different statistical analysis (imputation of missing values), but no justification was provided for this change in methods. This publication did not report any data on the operationalization "number of patients with at least 1 recurrence within the observation period".

Combining these 2 operationalizations of recurrence rate results in a hint of lesser benefit of cranberry in comparison with TMP-SMX.

Regarding the operationalization "number of patients with at least 1 recurrence within the observation period", the McMurdo 2009 study observed recurrence rates of 36.2% in the cranberry group and 20.6% in the antibiotics group (percentages calculated as part of this HTA report). A risk ratio of 1.616 ([95% CI: 0.93; 2.79]; p = 0.084; n = 137) was reported, indicating a non-significant difference.

For the recurrence rate, this results in no hint of greater or lesser benefit of cranberry in comparison with TMP.

Other PPs versus placebo

One study (Larsson 1993) reported data on the operationalization "number of patients with at least 1 recurrence within the observation period" for the comparison of UVA-E® (containing uva ursi leaves and dandelion root and herb) versus placebo. The recurrence rates across a 12-month period from treatment start were 0% in the UVA-E® group versus 23% in the placebo group. The between-group difference was reportedly statistically significant (significance level p < 0.05; no exact reporting of p-values; n = 57).

One study (Albrecht 2007) reported data on the operationalization "number of recurrences per study arm within the observation period" for the comparison of Angocin® (containing horseradish root and nasturtium herb) versus placebo. The mean number of recurrences per patient was 0.43 in the Angocin® group and 0.37 in the placebo group within the first 3 months after treatment start; for the entire study period of 6 months, it was 0.74 in the Angocin® group and 0.63 in the placebo group. The reported between-group differences were non-significant (3 months: p = 0.28; 6 months: p = 0.26; n = 174).

For the recurrence rate, this results in a hint of benefit for UVA-E® and no hint of benefit for Angocin® in comparison with placebo.

Other PPs + antibiotics versus antibiotics

One study (Sabadash 2017) reported data on the operationalization "number of patients with at least 1 recurrence within the observation period" for the comparison of Canephron® N (containing lovage root, rosemary leaves, and common centaury herb) in combination with ofloxacin versus ofloxacin. Recurrence rates were 8.9% in the Canephron® N group and 17.8% in the ofloxacin group within the first 6 months after treatment start and 15.5% in the Canephron® N group and 35.5% in the ofloxacin group within 12 months after treatment start. The between-group differences were reportedly statistically significant for both time points (significance level $p < 0.05$; no exact reporting of p-values; n = 90).

For the recurrence rate, this results in a hint of greater benefit of Canephron® N in combination with ofloxacin versus ofloxacin alone.

Cranberry preparations versus other PPs

In the Genovese 2018 study, the recurrence rate operationalized as "number of patients with at least 1 recurrence within the observation period" was compared between 3 treatment groups: DUTY® (containing uva ursi, birch, and barberry) in combination with D-mannose versus DUTY® S (containing uva ursi, birch, barberry, and makandi) in combination with D-mannose versus Cistiflux® plus (containing cranberry and D-mannose). Recurrence rates within the 6 months after treatment start were 16.7% in the DUTY® group (n = 24), 8.7% in the DUTY® S group (n = 23), and 29.2% in the Cistiflux® plus group (n = 24). No information was provided on the results' statistical significance.

For the recurrence rate, this results in no hint of greater or lesser benefit of any of the preparations in comparison with any other.

Cranberry preparation (monopreparation) versus cranberry preparation (combination preparation)

One study (Salinas-Casado 2020) reported data on the operationalization "number of patients with at least 1 recurrence within the observation period" for the comparison of Manosar® (containing PAC from cranberry, D-mannose, and other ingredients, see Table 12 of the full report) versus PAC from cranberry. The reported recurrence rates were 27.8% in the Manosar® group and 50% in the PAC group. The between-group difference was reportedly statistically significant ($p = 0.002$; n = 184).

For recurrence rate, this results in a hint of greater benefit of Manosar® in comparison with PAC.

4.5.5 Results on health-related quality of life

Data on health-related quality of life were reported by only 1 study (Bruyere 2019). This study surveyed quality of life by means of the SF-36 questionnaire [53] both at enrolment and at study end. The study's authors reported that no significant differences in quality of life were found between the 2 groups – DUAB® (containing cranberry extract, propolis, and zinc) versus placebo (no detailed results were reported).

For health-related quality of life, this results in no hint of benefit for DUAB® in comparison with placebo.

4.5.6 Results on adverse events

The data available on adverse events are unsuitable for pooled quantitative analyses or between-study comparisons because the information provided by the included studies is incomplete and varies greatly. Details are missing on data collection, such as whether any restrictions were placed (e.g. by collecting only treatment-related adverse events or focusing on a particular area), and any restrictions in place were not described in detail (e.g. by defining treatment-related adverse events). None of the studies reported the severity of the adverse events (based on a standardized scale). The reported results are therefore summarized only qualitatively below.

Cranberry preparations versus placebo

One study (Occhipinti 2016) reported no data on adverse events. One other study (Vostalova 2015) reported that no adverse events were observed in either study group, without providing any further information.

Two studies (Stothers 2002 and Takahashi 2013) reported some adverse events but failed to indicate whether they reported all events or only select events (e.g. treatment-related events). The Stothers 2002 study reported headache (2 of 50 patients) and nausea (2 of 50 patients) in the placebo group, reflux (3 of 50 patients) in the cranberry juice group, and nausea and frequent bowel movements (1 of 50 patients) in the cranberry tablet group. The Takahashi 2013 group reported that 1 of 106 patients in the cranberry group experienced a "strong burning sensation" following intake, while no adverse events were reported in the placebo group.

The Koradia 2019 study reported only treatment-related adverse events. In the cranberry group, 3 out of 44 patients had treatment-related adverse events (2 patients reported diarrhoea, 1 patient flatulence) versus 0 of 45 patients in the placebo group.

The Stapleton 2012 study accounted for the frequency of adverse events in general. In the cranberry group, 29 of 120 patients (24.2%) had adverse events, compared to 7 of 56 (12.5%)

in the placebo group. The reported between-group difference was not statistically significant (p = 0.7). The adverse events were reportedly mainly gastrointestinal and vaginal complaints and migraine.

Two studies (Bruyere 2019 and Maki 2016) reported data on severe adverse events, all of which were rated as not being treatment related (see Table 27 of the full report). Beyond this information, Bruyere 2019 stated only that tolerability was good in both study groups and no substantial differences were observed. Maki 2016 also reported the frequency of specific adverse events which occurred in at least 5% of patients. These frequencies did not substantially differ between the 2 groups (see Table 26 of the full report). Additionally, the Maki 2016 study used a questionnaire on gastrointestinal tolerability without describing the questionnaire in further detail. The study reported that 8 weeks after study start, significantly more patients in the placebo group reported increased nausea (1.6% in the cranberry group versus 5.9% in the placebo group; p = 0.044; n = 373). No further questionnaire results were provided. This results in no hint of harm from cranberry in comparison with placebo.

Cranberry preparations versus antibiotics

Both studies on the comparison of cranberry preparation versus antibiotics reported the frequencies of specific adverse events (see Table 26 of the full report). Beerepot 2011 reported general and severe adverse events separately. For both categories, the study concluded that no statistically significant differences in frequency were observed between the 2 groups (no detailed information provided). McMurdo 2009 reported that the frequencies of adverse events did not differ markedly between the groups. This results in no hint of lesser or greater harm from cranberry in comparison with TMP or TMP-SMX.

Other PPs versus placebo

The Larsson 1993 study reported, without providing detailed information, that no adverse events were observed in either study arm – UVA-E® (containing uva ursi leaves and dandelion root and herb) versus placebo. The Albrecht 2007 study reported that 36 of 84 patients in the Angocin® group (Angocin® contains horseradish root and nasturtium herb) and 37 of 90 patients in the placebo group had adverse events. The observed adverse events were listed without providing information on the frequencies in the groups (see Table 28 of the full report). There was reportedly no statistically significant difference between the 2 groups. In addition, severe adverse events were reported in both groups, with all of them rated as not being treatment-related (see Table 27 of the full report). The study therefore shows no hint of harm from UVA-E® or Angocin® in comparison with placebo.

Cranberry preparations versus other PPs

The Genovese 2017 study reported, without providing any further detail, that no adverse events were observed in any of the 3 study arms – DUTY® (containing uva ursi, birch, and

barberry) in combination with D-mannose versus DUTY® S (containing uva ursi, birch, barberry, and makandi) in combination with D-mannose versus Cistiflux® plus (containing cranberry and D-mannose). This results in no hint of greater or lesser harm from any of the preparations in comparison with any other.

Cranberry preparation (monopreparation) versus cranberry preparation (combination preparation)

The Salinas-Casado 2020 study comparing Manosar® (containing PAC from cranberry, D-mannose, and other ingredients, see Table 12 of the full report) versus PAC from cranberry reported that 12 of 90 patients in the Manosar® group and 19 of 94 patients in the PAC group experienced adverse events. The most common adverse events were reported in detail for both groups, showing that they did not differ substantially (see Table 26 of the full report). Hence, there was no hint of greater or lesser harm from Manosar® in comparison with PAC.

4.5.7 Results on mortality

Mortality data were explicitly reported by only 1 study (Koradia 2019). In this study, 0 deaths were reported for both study arms (BKPro-Cyan versus placebo). This results in no hint of benefit or harm from BKPro-Cyan in comparison with placebo.

4.6 Evidence map

Table 4 below shows the evidence map regarding patient-relevant outcomes.

Table 4: Evidence map regarding patient-relevant outcomes

	Mortality	Morbidity					QoL
	All-cause mortality / overall survival	Specific symptoms	Time until recurrence	Recurrence rate	Development of complicated infections	AEs	Health-related quality of life (SF-36)
Cb preparations vs. placebo							
Cb preparations vs. placebo	⇔	-	⇗	⇑	-	⇔	⇔
Cb preparations vs. antibiotics							
Cb preparations vs. TMP	-	-	⇔	⇔	-	⇔	-
Cb preparations vs. TMP-SMX	-	-	⇘	⇘	-	⇔	-
Other PPs vs. placebo							
Angocin® vs. placebo[c]	-	-	-	⇔	-	⇔	-
UVA-E® vs. placebo[d]	-	-	-	⇗	-	⇔	-
Other PPs + antibiotics vs. antibiotics							
Canephron® N in combination with ofloxacin vs. ofloxacin[e]	-	⇔	-	⇗	-	-	-
Cb preparations vs. other PPs							
DUTY® vs. DUTY® S vs. Cistiflux® plus[f]	-	-	-	⇔	-	⇔	-
Cb preparations vs. Cb preparations							
Manosar® vs. PAC[g]	-	-	⇔	⇗	-	⇔	-

⇑: indication of (greater) benefit

⇗: hint of (greater) (added) benefit

⇘: hint of lesser benefit

⇔: no hint, indication, or proof

-: no data reported

c. Angocin® contains horseradish root and nasturtium herb.

d. UVA-E® contains uva ursi leaves as well as dandelion root and herb.

e. Canephron® N contains lovage root, rosemary leaves, and common centaury herb.

f. DUTY® contains uva ursi, birch, and barberry; DUTY® S contains uva ursi, birch, barberry, and makandi; Cistiflux® plus contains cranberry and D-mannose.

g. Manosar® contains cranberry and D-mannose.

Cb: cranberry; PAC: proanthocyanidin; QoL: quality of life; TMP: trimethoprim; TMP-SMX: trimethoprim-sulphamethoxazole

5 Results: Health economic assessment

5.1 Intervention costs

It was impossible to determine in a standardized manner the intervention costs of all preparations in question because some PPs are classified as medicinal products, while others are deemed dietary supplements or foods. Therefore, the authors selected the interventions (and comparator interventions) which were investigated in the studies included for the benefit assessment and are (currently) available on the German market. They included various cranberry products (some combined with other dietary supplements e.g. propolis, zinc, or D-mannose), 2 combination preparations with other herbal remedies (horseradish root and nasturtium; powder of centaury herb, lovage root, and rosemary leaf), and 2 antibiotics. All substances were used for recurrence prevention. For 1 of the 2 antibiotics, the Summary of Product Characteristics (SPC) requires monitoring blood count during treatment.

Sources for the cost determination were the Lauer-Taxe pharmaceuticals database (LAUER-TAXE® Online 4.0 [54]), the Uniform Value Scale (EBM) [55], and prices indicated by online pharmacies and mail order businesses. Sources used for quantity structures were the information provided by the RCTs included in the benefit assessment and the SPCs [56–59] (in consultation with the involved clinical expert). In the RCTs, treatment length for recurrence prophylaxis ranged from 3 to 12 months, while the S3 guideline does not issue an explicit recommendation for PPs. The consulted clinical expert stated that, in practice, a treatment length of half a year can be presumed. A half year of prophylactic use of products containing cranberry costs patients about €60 to €190 for cranberry-only products and €150 to €270 for combination products. The costs of the 2 other herbal combination preparations equal about €120 and €320. These costs are likewise to be paid by patients, but since said preparations are classified as medicinal products, some health insurance funds may reimburse them as optional benefits. The 2 antibiotics are associated with semi-annual costs of almost €125 to €130 (cotrimoxazole) and about €80 (trimethoprim), which are covered by the health insurance except for a patient copayment. The higher costs of cotrimoxazole are due to blood count monitoring being necessary during treatment.

5.2 Systematic review of health economic evaluations

5.2.1 Results of the information retrieval

The various search steps found a total of 3 relevant studies: Stothers 2002 [48], Bosmans 2014 [52], and Eells 2014 [60].

The search strategies for bibliographic databases are found in the appendix. The last search was conducted on 27 November 2020.

Table 5: Study pool for the health economic assessment

Study	Available documents [reference]
Bosmans 2014	[52]
Eells 2014	[60]
Stothers 2002	[48]

5.2.2 Characteristics of the studies included in the assessment

All 3 health economic evaluations investigated recurrence prophylaxis with cranberry preparations in patients with recurrent lower UTIs who are not experiencing acute symptoms (≥ 2 [Stothers 2002], ≥ 3 [Bosmans 2014] or 3 [Eells 2014] lower UTIs annually). All of these calculations are based on a 12-month period, for which they determine cost per prevented lower UTI (cost–effectiveness analysis). Two studies (Bosmans 2014 and Eells 2014) also compare costs and quality-adjusted life years (QALYs) (cost-utility analysis). All analyses account for direct (medical and nonmedical) costs, irrespective of their reimbursability; Bosmans 2014 additionally included indirect costs in a scenario analysis.

The oldest publication, Stothers 2002, a health economic evaluation accompanying an RCT (reported in the very same publication) compared 2 **cranberry products** – tablets with concentrated cranberry juice twice daily and 250 mL unsweetened, undiluted cranberry juice thrice daily – **with placebo**. The study was conducted in Canada.

The Bosmans 2014 study is another health economic evaluation accompanying an RCT (Beerepot 2011); it compares daily use of 500 mg **cranberry extract versus** 480 mg of the antibiotic **trimethoprim-sulphamethoxazole**. The study was conducted in the Netherlands. The utility values for QALY calculation were converted from the quality-of-life data surveyed in the RCT (for details, see Section A4.2.2 of the full report).

A decision analytical model (Eells 2014; Markov model) compared daily **cranberry tablets versus a total of 5 other measures**: acupuncture (monthly), oestrogen prophylaxis (daily), 100 mg nitrofurantoin (daily), symptomatic self-medication (in yeast infection), and no prophylaxis. The reference country was the United States. Alternatives were selected based on a systematic literature search in the MEDLINE, Embase, and Cochrane databases (1966–2012). Included were only measures investigated by at least 2 included studies. In the model, these studies also served as the source for the benefit outcomes. For “important outcomes”, the utility values for calculating QALYs were estimated using values from the literature (without detailed explanation). The authors investigated 2 cost perspectives separately: the perspective of public payers (in the healthcare system) and the perspective of patients. They assumed the cost of prophylaxis with cranberry and acupuncture to be fully borne by patients,

while for all other services, patients were responsible for copayments only (without providing further breakdowns).

5.2.3 Results and limitations of the health economic evaluation

After converting into € and inflation-adjusting to the year 2020, the study comparing 2 **cranberry products versus placebo** (Stothers 2002) calculated costs of €1627 for preventing 1 lower UTI by cranberry tablet prophylaxis and costs of € 2869 for the prevention of 1 lower UTI by cranberry juice prophylaxis, both compared to placebo. The author cites as limiting factors that (a) placebo juice and cranberry juice were not exactly comparable, (b) the exact substance concentration might have varied between different product batches, and (c) adherence was surveyed only via self-report. Met with further criticism is the fact that the cost perspective was not clearly identified or justified in the publication, neither cost data nor their sources were transparently identified, and that no information was provided on the year the costs arose (2001 was assumed to be the cost year for inflation adjustment). Likewise, no information was provided on the handling of uncertainties – no sensitivity analyses were reported. Due to costs having been surveyed in a different healthcare system, they cannot be directly extrapolated to Germany.

The comparison of lower UTI prophylaxis by means of 500 mg **capsules of cranberry extract** versus antibiotic prophylaxis (**trimethoprim-sulphamethoxazole**) (Bosmans 2014) showed that, for prophylactic purposes, cranberry capsules were more expensive than antibiotics and simultaneously prevented fewer lower UTIs; patient satisfaction and the calculated gain in QALYs were likewise lower for cranberry prophylaxis. Scenario analyses showed the same results. As limiting factors, the authors cite the study's high drop-out rate and the fact that it did not account for costs resulting from increased antibiotic resistance. Resistant bacteria can (a) spread and increase costs to be borne by the insured community and (b) require more expensive treatment for the individual patient. The authors also mention that the optimal dose for cranberry prophylaxis has yet to be determined and that the study might have used an excessively low dose. Further criticisms include that the publication failed to clearly identify or justify the cost perspective or to present the (amounts and survey methods for) intervention costs. Also, no justification was provided for excluding the costs of side effects from the basic-case analysis and including them only in a scenario analysis. Due to the costs being recorded in a different healthcare system, they are not directly transferable to Germany.

The broader comparison (Eels 2014) of lower UTI prophylaxis on the basis of 6 different interventions – **cranberry tablets, acupuncture, oestrogen treatment, nitrofurantoin, self-medication of symptoms, and no prophylaxis** – showed that nitrofurantoin prophylaxis prevented the largest number of lower UTIs per patient and year, followed by acupuncture, oestrogen, and cranberry; the results were similar for the ranking of QALYs (for details, see Section A4.2.3 of the full report). From the perspective of public payers, cranberry tablets

were associated with lower costs than no prophylaxis and simultaneously reduced the frequency of lower UTIs. The study's authors did not calculate a direct comparison of cranberry versus the other alternatives. The results show that cranberry was both more expensive and more effective than self-medication, but less expensive and less effective than nitrofurantoin. Compared with oestrogen prophylaxis, cranberry was less expensive (and similarly effective); compared with acupuncture, it was more expensive and less effective (for details, see Table 40 of the full report). The cost of cranberry prophylaxis from the patient perspective is presented only in a supplement which is not available (any longer). In the sensitivity analysis, the cost parameters deemed by the study authors to be most influential from the perspective of the payors were those incurred by oestrogen prophylaxis and antibiotic prophylaxis, and from the patient perspective, these were those incurred by cranberry prophylaxis and acupuncture prophylaxis (for further details, see Section A4.2.3 of the full report). The authors list multiple limitations: Among other things, various factors such as antibiotic resistance, medication adherence, and rare side effects were not explicitly accounted for. Some of the underlying clinical studies suffered from methodological limitations, and the results on benefit were potentially subject to publication bias since only results of published studies were taken into account (including 2 on acupuncture, 4 on cranberry, 5 on oestrogen, 6 on antibiotics, and 3 on self-medication). However, the authors did not methodologically discuss the calculations performed on the quantitative synthesis of benefit assessment in further detail. It should also be noted that only studies comparing with placebo or no treatment were included, and the quality of these studies was not discussed any further. There is no report of a model validation being conducted. Due to costs having been surveyed in a different healthcare system, they cannot be directly translated to Germany. Likewise, the inclusion criteria for the underlying clinical studies differ from those of this HTA report's benefit assessment, e.g. regarding study design.

In summary, this results in greater effectiveness and higher costs for cranberry prophylaxis compared to placebo (Stothers 2002), with cranberry prophylaxis even being dominant to the alternative of no prophylaxis in another study which accounted for costs only from the perspective of public payers (Eells 2014). Compared to antibiotic prophylaxis, cranberry prophylaxis was associated with both lower effectiveness and higher costs (Bosmans 2014). When accounting for costs only from the public payer perspective, however, cranberry prophylaxis is less expensive than antibiotic prophylaxis (Eells 2014). Alongside poor transferability, studies exhibit marked deficiencies in quality and transparency. Therefore, the identified health economic evaluations are of very limited use for assessing cost effectiveness in the present HTA report.

6 Results: Ethical, social, legal, and organizational aspects

6.1 Results on ethical aspects

Worldwide, symptomatic lower UTS are among the most prevalent infectious diseases predominantly affecting women [16]. Recurrent lower UTIs in women can lead to substantial individual suffering, adversely impact affected people's quality of life, and furthermore exhibit socially relevant aspects [62–64]. Simultaneously, uncomplicated cystitis is among the most common grounds for prescribing antibiotics [65]. Antibiotic resistance represents a worsening global problem viewed as one of the major challenges faced by our healthcare systems and is associated with increasing costs [1,66,67]. With this in mind, the assessment of ethical and social aspects focused in particular on the problem of antibiotic resistance.

The literature search identified no studies explicitly addressing ethical aspects or principles regarding herbal preparations for in bladder infections. However, studies included in the ethical and social analysis (see references in Table 43 through Table 45 of the full report) which investigate the use of herbal preparations, including for treating uncomplicated bladder infection, are related to ethical principles and social aspects. Furthermore, studies are available which investigate antibiotic resistance in general from an ethical perspective [66,68].

One relevant aspect is the principle of autonomy, for instance. It involves the duty to respect individuals' autonomous decisions and to support their ability to lead a self-determined life. Some studies note that women like to forego antibiotics if they are made aware of alternative treatment options [65,69]. But at the same time, they point out that women sometimes do not feel taken seriously if they are not prescribed antibiotics [65]. Accordingly, both a prospective cohort study in Germany and a household survey in England reported that only about 60% of women who were prescribed antibiotics for uncomplicated lower UTIs actually took them [14,70]. The use of herbal remedies often suits users' personal views of health and disease as well as their need for autonomy and self-care [71]. At the same time, users of herbal remedies often know little about interactions with other medications [72]. Empowering patients to make autonomous decisions requires sensitively responding to patient preferences and is essential for joint decision-making concerning therapeutic options [65,69,70,73,74]. In this case, following the principles of "duty of care" or "beneficence" [28] as well as weighing risks versus benefits would require including herbal alternatives as an integral part of the treatment and prevention of uncomplicated cystitis, provided evidence of their effectiveness is available and said evidence is transparently communicated [61,65,66]. Promoting healthcare providers' knowledge and skills regarding herbal remedies might facilitate patient access to evidence-based consultation [72]. This could, in part, prompt affected women to choose herbal remedies which come with at least indications of a benefit, while also affirming the women in their need for autonomy. The importance of participative

decision-making, particularly regarding antibiotic therapy, is also emphasized by the S3 guideline issued by the German Society of Urology [1].

Alongside the weighing of benefit versus harm on an individual patient level, the choice of cystitis treatment affects society as a whole due to the increasing spread of resistant bacterial strains. A judicious, sparing use of antibiotics is also a relevant aspect of (intergenerational) justice because future patients have a right to be protected from the harm of antibiotic resistance [68]. In summary, a conflict may develop between the present individual benefit and the societal perspective; this should be transparently communicated to patients in the context of them being autonomous agents.

6.2 Results on social aspects

The employed search criteria returned 5 studies explicitly investigating social aspects. These studies highlight both societal and individual burdens associated with recurrent lower UTIs [62-64,75,76]. Societal burdens include, e.g. economic burdens due to loss of working hours, doctor visits, and comorbidities. Cited personal strains include clinical burdens, limitations in everyday activities and at work, poor concentration, and anxiety which may have social and psychological consequences and negatively impact quality of life. Likewise, recurrent lower UTIs can be associated with substantial individual and societal costs [63,76]. The social effects of recurrent lower UTIs can be particularly pronounced in premenopausal working women [63]. Medina et al. point out that merely treating a lower UTI is often insufficient for improving a patient's quality of life. The frequently neglected effects of treatment on quality of life should therefore be taken into account when evaluating treatment effectiveness [63]. Appropriate prophylaxis is also very important with regard to both patients' quality of life and societal burdens [63].

In terms of social aspects, the affordability of herbal remedies plays an important role, including with regard to the ethical principle of justice. Many women would like to forego or delay the use of antibiotics if they are made aware of this option [65,73]. However, the costs of herbal remedies are typically paid out of pocket by the patient (see also Section 6.3) [65,72]. For patients, financial aspects may therefore play a role in the choice of therapy. This aspect was addressed by all interview partners surveyed as part of the research on this HTA (see Section A6.2 of the full report). During the research on this HTA, it further became evident that herbal remedies are marketed under different categories, e.g. as pharmaceuticals, dietary supplements, and foods. As a consequence, their packaging, advertising, and provided information (e.g. regarding contents and effect) can differ considerably. This makes it difficult for affected people to obtain pertinent information. Making available independently researched, evidence-based, transparently presented information in an easily accessible manner, e.g. on relevant websites, would be helpful for affected people. The results of the patient survey suggest that patients are willing to try a wide range of options for managing

recurrent bladder infections and that, for this purpose, they rely on information provided by physicians and pharmacies as well as from their friends and family and the Internet (see Section A6 of the full report). To support adequate self-management by affected women requires good communication and education as well as availability of a physician [65,70,74].

6.3 Results on legal aspects

6.3.1 Herbal medicinal substances

Definition

According to Section 2 (1) German Medicinal Products Act (AMG), a medicinal product is any substance or combination of substances intended for curing, alleviating, or preventing diseases or disease symptoms (medicinal product by presentation) or administered to make a medical diagnosis or to restore, correct, or influence physiological functions through a pharmacological, immunological, or metabolic effect (medicinal product by function) [77].

This definition implements Article 1 of Directive 2001/83/EC (Community code relating to medicinal products for human use) into German law. As per Section 4 (29) AMG, herbal medicinal products are medicinal products which exclusively contain, as active substances, either one or more herbal substances, one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. [77]

Marketing authorization

According to Section 13 (1) AMG, manufacturing medicinal products requires a permit. The permit, in turn, requires a favourable result of the medicinal product's clinical investigation in accordance with Section 21 AMG. In the context of this investigation, the effect of the medicinal product must have been favourably assessed, with particular attention being paid to side effects and interactions. In Germany, the Federal Institute for Drugs and Medical Devices is responsible for marketing authorizations.

Regarding phytotherapeutics, which require a marketing authorization like all medicinal products, the AMG provides for various approval procedures in accordance with the available scientific evidence. They include the same regulatory dossiers as are used for medicinal products on a synthetic basis, but also some procedures specifically designed for herbal medicinal products:

- Complete dossier:

For an herbal medicinal product to be unconditionally approved, the same scientific proof of efficacy must be supplied as for the approval of a synthetic medicinal product. This includes double-blind studies conducted with appropriate methods and a sufficiently large number of patients [78].

- Bibliographic dossier:

Alternatively, a special type of application for marketing authorization requires no submission of preclinical or clinical data. The prerequisite for using this alternative is that the active substances of the herbal medicinal product (a) have been used for medicinal purposes in the European Union for at least 10 years and (b) exhibit known effects and an acceptable level of safety. To demonstrate this, the relevant preclinical and clinical aspects of the medicinal product must have been presented in publicly accessible and recognized sources [78].

- Registration as a traditional herbal medicinal product:

Another option is registering phytotherapeutics as traditional medicinal products. This process requires demonstrating effectiveness not through product-specific clinical trials but through "traditional documentary evidence" on the basis of which effectiveness is deemed plausible. This requires that the preparation has been used for medical purposes for at least 30 years; additionally, it must have been in use in the EU for at least 15 years at the time the application is submitted. Registration as a traditional herbal medicinal product is possible only if the product is intended for use without supervision by a medical practitioner, i.e. for diagnostic purposes, for prescription, or for monitoring of treatment. In addition, the registered strengths or dosages must be safe, and the preparation must be applied orally, externally, or by inhalation.

Reimbursement and use

SHIs are required to reimburse medicinal products only if the products are pharmacy- and prescription-only medicinal products. Medicinal products which are not pharmacy-only and those which are pharmacy-only but not prescription-only are therefore excluded from reimbursement [77].

The majority of herbal medicinal products, including medicinal products used to treat urocystitis, is not prescription-only and therefore not reimbursable. Since 2012, however, Section 11 (6) SGB V allows health insurance funds to offer their insured members various optional benefits, provided said benefits have not been excluded by the Federal Joint Committee (G-BA). These optional benefits can include also non-prescription, pharmacy-only medicinal products. Hence, these medicinal products can be reimbursed by health insurance funds on a voluntary basis, with most insurance funds defining an annual budget per insured person. According to an overview by the German Pharmaceutical Industry Association (BPI), in 2021, about 70 of the 103 SHIs in Germany reimbursed non-prescription medicinal products, with the majority focusing on herbal, homoeopathic, and anthroposophic over-the-counter drugs [79].

6.3.2 Dietary supplements

Medicinal products are not the only products containing herbal substances. Other product groups with similar properties exist but are subject to different legal requirements. One example are dietary supplements, which are much less strictly regulated but are often sold in forms typical for medicinal products, e.g. as tablets. While it is impossible to assign the same product to 2 product groups at the same time, products with very similar properties might indeed be found in different groups [80]. Distinguishing product groups is often difficult for users/patients and professionals alike [81].

Definition

Section 1 of the German Food Supplements Ordinance (NemV) defines dietary supplements as foods characterized by 3 properties [82]:

1) Purpose: They are intended to supplement the general intake of food.
2) Composition: They contain a concentrate of nutrients or other substances having a nutritional or physiological action, alone or in combination.
3) Dosage form: They are marketed in metered form, in particular in the form of capsules, lozenges, tablets, pills and other similar dosage forms, powder sachets, liquid ampoules, etc.

According to Section 1(2) NemV, “nutrients” refer to vitamins and minerals (including micronutrients), while “other substances having a nutritional or physiological action” include amino acids, essential fatty acids, dietary fibre, plant and herbal extracts, etc.

Marketing authorization

Being defined as foods, dietary supplements are subject to the corresponding general requirements of food law, with the most important provisions being found in Article 14 of Regulation (EC) No 178/2002 (Basic Regulation). The latter states that all foods placed on the market must be safe and hence must not be injurious to health. According to Article 17 of the Basic Regulation, food and feed business operators are primarily responsible for ensuring food safety [83]. Dietary supplements are not subject to approval involving a benefit-risk assessment as is the case for medicinal products.

The specific legal provisions applying to dietary supplements are laid down by NemV, which implements EU Directive 2002/46/EC into German law. The regulation contains provisions about the vitamins, minerals, and their combinations allowed in dietary supplements as well as notification and labelling requirements [82]:

- Substances allowed in dietary supplements

- The nutrients, i.e. vitamins and minerals and their combinations, which may be used in dietary supplements are defined EU-wide. They are listed in Annexes I and II of Directive 2002/46/EC.
- However, the rules differ and are less specific for plant and herbal extracts which fall under the category of “other substances having a nutritional or physiological action”. For these “other substances” in dietary supplements, neither negative nor positive lists exist; only 2 substances are prohibited by the Enrichment Regulation (Regulation [EC] No 1925/2006).

- Notification requirement
  - The notification requirement specifies that a manufacturer or importer must notify the competent authority, i.e. the German Federal Office of Consumer Protection and Food Safety (BVL), of the dietary supplement no later than when it is first placed on the market.
  - The notification of the dietary supplement is reviewed and forwarded to the German Federal Ministry of Food and Agriculture as well as to the highest authorities at the federal state level in charge of food surveillance. However, the dietary supplement may be placed on the market at the time the notification is provided.
- Labelling regulations
  - With regard to the labelling of dietary supplements, both Regulation (EU) No. 1169/2011 and NemV apply. For instance, dietary supplements must be referred to only as such (Regulation [EU] No. 1169/2011) and the names of the nutrients or other substances as well as the recommended daily intake must be identified.
  - The label must also include a statement that taking the product does not replace a balanced and varied diet.
  - It is also stipulated that advertising of dietary supplements must not attribute to them the property of curing, alleviating, or preventing a disease and must not make them appear to be medicinal products.

Reimbursement

Dietary supplements are excluded from health services; therefore, they are generally not reimbursed by health insurance funds and must be paid by the patient out of pocket [84].

6.4 Results on organizational aspects

The scoping search revealed 6 documents and other sources regarding organizational aspects of the use of phytopreparations in adult patients in Germany. They were found exclusively through the manual search in sources outside of MEDLINE.

Herbal medicinal substances or dietary supplements for the treatment of lower UTIs are taken in the form of tablets, capsules, juices, or tea, and treatment can be carried out by patients independently at home. The respective herbal medicinal substances or dietary supplements are freely available and hence easily accessible, although their costs are typically paid out of pocket (see Section 6.3). Phytopreparations may be recommended by physicians in the context of common examinations; hence, no changes result regarding the prerequisites of service provision or changes with regard to structural quality.

In Germany, it is safe to assume a generally high patient acceptance of phytopreparations. Alternative treatment options for lower UTIs are viewed as attractive and are presumably well accepted [65,69,72]. With regard to physician attitudes towards phytopreparations, the only studies found investigated recommendations of herbal medicinal substances across therapeutic indications [85,86]. These studies suggest that the use of herbal medicinal products is commonly recommended by general practitioners; the same presumably applies to the treatment of bladder infections.

7 Synthesis of results

The evidence available from RCTs answers the question of whether PPs are effective **only to a limited extent and only for certain substances**. No RCTs are available for many of the PPs relevant for this HTA report (see overview in Table 1).

The largest amount of data is available for cranberry preparations. These data show an **indication of benefit for cranberry in comparison with placebo regarding a reduction in the recurrence rate**. The available studies investigated various cranberry preparations of different compositions. It is **impossible to conclusively determine whether the study results can be extrapolated to all available preparations containing cranberry**. Concerning the other investigated PPs, there are hints of benefit for a preparation from uva ursi leaves and dandelion in comparison with placebo as well as hints of added benefit of a preparation made of lovage root, rosemary leaves, and common centaury herb (in combination with antibiotics) versus antibiotic monotherapy for recurrence prevention. Notably, only a single one of the 15 studies included in this HTA reported results on the outcome of health-related quality of life despite the fact that recurrent bladder infections can be associated with substantial personal burdens for patients (see Sections 4.3 and 6.2) [63,76]. The available studies provided no hint of PPs being effective in reducing specific symptoms in women with recurrent uncomplicated lower UTIs. Therefore, **no conclusions can be drawn on the effectiveness of PPs in the acute care of lower UTIs** in this group.

The S3 guideline issued by the German Society of Urology recommends prevention with long-term antibiotic therapy (for 3 to 6 months) only “after failure of the general preventive measures and nonantibiotic therapies [...] in patients with a high level of suffering” [...]. Against this background, the question regarding the effectiveness of **PPs in comparison with antibiotics for long-term prevention is particularly relevant for a limited subpopulation** of women with recurrent uncomplicated lower UTIs. In this comparison, a hint of lesser benefit was found for cranberry extract in comparison with the combined antibiotics TMP-SMX regarding the prevention of recurrences.

Unlike in long-term prevention, the S3 guideline recommends the **prescription of antibiotics in the acute care of lower UTIs**, provided antibiotic stewardship and participative decision-making with patients are practised [1,15]. Studies as well as prescription data indicate that in practice, antibiotics are frequently prescribed for lower UTIs (see Section 1.3) [13,14]. Patient interviews confirm this impression. Frequent prescription of antibiotics is associated with risks not only on the individual level but particularly on a societal level due to the **development and spread of resistant bacterial strains**. The World Health Organization has classified multidrug-resistant bacterial strains as one of the greatest challenges for public health [67]. The identified health economic studies likewise point out that antibiotic resistance is associated with societal costs which were not quantifiable in the context of these studies

[48,52,60]. No data are available from RCTs for comparing the effectiveness of PPs versus antibiotics in the acute care of lower UTIs.

Studies as well as patient interviews show that many patients have a positive attitude towards PPs and would like to treat their lower UTIs without antibiotics if a suitable herbal alternative is available. Most of the PPs which were investigated in the studies for the benefit assessment and are available in Germany are classified as foods – typically in the subgroup of **dietary supplements** – and are therefore **completely excluded from reimbursement**. Unlike antibiotics, even the 2 preparations classified as medicinal products are non-prescription products and are therefore reimbursable only as an optional benefit by certain health insurance funds. Hence, **financial aspects may affect patients' treatment choices**. Long-term prevention with the preparations investigated in the benefit assessment or comparable products available in Germany costs about **€60 to €320 for herbal preparations and about €80 to €130 for antibiotics, at an assumed treatment duration of 6 months**, with patients paying about one-fourth of the antibiotics costs in the form of a copayment.

Patients are confronted with a **very nontransparent market** of herbal medicinal products and dietary supplements. While dietary supplements are not to be advertised with claims about them curing, alleviating, or preventing diseases, such advertisements are sometimes seen in practice [87,88].

8 Discussion

8.1 HTA report compared with other publications

The systematic reviews screened for this HTA report were checked regarding the included primary studies in order to identify any other studies potentially relevant for the benefit assessment. Other than that, the existing systematic reviews were neither systematically analysed nor checked for methodological quality. In summary, however, the reviews on the effectiveness of cranberry for treating uncomplicated recurrent lower UTIs arrive at similar conclusions as this HTA report. While some of the performed metaanalyses suggest its effectiveness, the results suffer from uncertainties due to various limitations. Among others, they include the fact that the investigated dosages differed and were not clearly described, and that the definitions of lower UTIs and recurrence differed [89,90]. The included health economic studies also emphasized that dosages were unclear, resulting in limited comparability [48,52,60]. These studies referred only to cranberry prophylaxis, for which they demonstrated lower effectiveness and higher total costs for cranberry compared to antibiotic prophylaxis – albeit disregarding the cost effects of antibiotic resistance – as well as higher effectiveness and higher cost of cranberry compared to no prophylaxis.

8.2 HTA report compared with guidelines

The S3 guideline issued by the German Society of Urology deems the available evidence on PPs in the treatment of lower UTIs to be insufficient. Study data on cranberry were evaluated as being contradictory, and therefore, no recommendation was issued for cranberry (see acknowledgement of the comment in Section A7.6 of the full report). Further, it was noted that various PPs may be options for women with recurrent lower UTIs, but no specific recommendations were issued for specific PPs [1].

8.3 Critical reflection on the approach used

On the basis of the concerns of those proposing the topic, the focus of this HTA report was limited to women with recurrent lower UTIs. Regarding the question on effectiveness in the acute treatment of symptomatic episodes and considering the lack of study data for this population, no conclusion can be drawn (see outcome on specific symptoms). This, however, is a highly relevant question both for patients and for society due to the potential avoidance of antibiotic use. Data from studies which investigated the efficacy in lower UTIs in general – not restricting the investigated population to women with recurrent UTIs – might be relevant for the population in question as well, but they were not investigated in the present HTA report. However, it is conceivable for the effectiveness of PPs to differ in the acute treatment of lower UTIs in general versus in the acute treatment of symptomatic episodes in women with recurrent lower UTIs – and this question would likewise need to be investigated in studies.

RCTs were available for only some of the relevant PPs, and PP manufacturers might have little incentive to conduct time-consuming and expensive clinical studies since proof of effectiveness is not necessary for marketing these products. Therefore, additional information might conceivably be obtainable from non-randomized studies (e.g. observational studies).

The various PPs to be investigated in this HTA report were compiled on the basis of the S3 guideline issued by the German Society of Urology, a registry published by the EMA, and input from a urologist and a pharmacist working in Germany. Therefore, all PPs relevant for the German market should be included in the list. Conceivably, however, studies not included in this HTA report might contain data on PPs available to patients in Germany via online purchase, etc. On the other hand, the systematic literature search did use both the selected PPs and general search terms such as phytotherapy as key terms. Only a single study was excluded solely because it investigated a different PP [91].

8.4 Dosing of cranberry preparations

A difficulty in assessing the benefit of cranberry preparations lies in the fact that several randomized studies are available, but no precise information is provided on the dosage of the preparations available or investigated in the studies. This issue was also emphasized by health economic studies and reviews [48,52,60,89]. While herbal medicinal products – unlike synthetically manufactured preparations – are subject to natural variations, uncertainties regarding dosage and composition could nevertheless be reduced by providing exact information on the manufacturing process. One way to standardize cranberry products would be to provide information on their content of PACs, which, based on microbiological experiments, are believed to cause the potential effects of cranberry. While said information was provided in some of the included studies, the procedures for determining PAC content differ, potentially yielding different results [39]. The studies lacked precise descriptions of measuring methods. Furthermore, it should be noted that even if uniform dosages are used, the bioavailability of PACs or other cranberry constituents might vary between dosage forms (e.g. juices versus tablets). A current study published after completion of the systematic literature search for this HTA report investigates the efficacy of different PAC-standardized dosages of cranberry preparations [92]. Future studies on this basis might allow drawing more definitive conclusions on the benefit of cranberry.

9 Conclusion

The benefit of phytopreparations in comparison with different or no treatment in adult women with uncomplicated recurrent lower UTIs was investigated by 15 studies meeting this HTA report's inclusion criteria. Among the 34 plants (or part components) which had been predefined as being relevant for this HTA report, 9 were investigated in the included studies.

Most studies examined preparations containing cranberry. This results in an indication of benefit for cranberry in comparison with placebo regarding the reduction of recurrence rate and a hint regarding the extension of the interval until the first recurrence. There is a hint of lesser benefit of cranberry regarding recurrence prevention when compared with antibiotics, specifically trimethoprim sulphamethoxazole. Aside from cranberry, isolated study results are available on preparations containing the following plants (or plant components): 1 preparation with horseradish root and nasturtium herb, 1 preparation with uva ursi leaves and birch, 1 preparation with uva ursi leaves and dandelion, and 1 preparation with lovage root, rosemary leaves, and common centaury herb. The assessment found a hint of benefit for a preparation made from uva ursi leaves and dandelion in comparison with placebo as well as a hint of added benefit (in combination with antibiotics) of a preparation made of lovage root, rosemary leaves, and common centaury herb versus antibiotic monotherapy for recurrence prevention. Very few data are available for the outcomes of health-related quality of life, development of complicated infections, specific symptoms, and mortality. For mortality and health-related quality of life, this results in no hint of benefit for cranberry preparations in comparison with placebo. For specific symptoms, there is no hint of benefit for a preparation made of lovage root, rosemary leaves, and common centaury herb in combination with antibiotics when compared with antibiotic monotherapy. No further conclusions on benefit can be drawn regarding these outcomes.

No adverse events data are available for comparing a preparation made of lovage root, rosemary leaves, and common centaury herb in combination with antibiotics versus antibiotic monotherapy; no conclusion can be drawn on benefit. For all other comparisons investigated herein, the reported adverse events show no hint of greater or lesser harm from one of the investigated preparations in comparison with the respective comparator intervention.

The transferability of the benefit assessment's results to Germany is limited by the fact that not all herbal preparations investigated in the benefit assessment correspond to commercial products available in Germany. More than half of the cranberry monopreparations and 2 of the preparations without cranberry (uva ursi leaves and birch as well as uva ursi leaves and dandelion) were either impossible to find, inadequately described, or no longer (if ever) available on the market.

With regard to the determination of costs, the available studies and data placed the focus on long-term prevention. Among the investigated phytopreparations, the cost of 6 months of treatment with these foods or dietary supplements ranged from €60 to €270; these costs must be borne by the patients out of pocket. For other herbal medicinal products which were classified as pharmaceuticals by the LAUER-TAXE® pharmaceuticals database, costs equalled €110 to €300; some of these costs were covered by health insurance companies on a case-by-case basis. For "general preventive measures and non-antibiotic therapies" which, according to the S3 guideline, are to be exhausted before potentially initiating long-term preventive antibiotic treatment, prevention with phytopreparations therefore incurs potential semiannual costs to be paid by patients in the two-digit to low three-digit range. For 6 months of long-term preventive therapy with antibiotics, in contrast, patients incurred costs of (a maximum of) about €20 to €35 (at total costs of up to €130).

According to cost effectiveness literature on cranberry prophylaxis (compared with placebo), the enhanced effectiveness with respect to recurrence prevention is juxtaposed by higher direct costs. Cranberry's lower effectiveness in recurrence prevention when compared with antibiotic prevention is paired with higher cost (than antibiotics), making cranberry prophylaxis the predominant alternative over antibiotics. However, this calculation ignored the potential costs of antibiotic resistance. Due to poor transferability and substantial deficiencies in quality and transparency, however, the identified health economic evaluations are of very limited use for assessing cost effectiveness in the present HTA report. In any case, important factors influencing the cost effectiveness of cranberry prophylaxis in comparison with antibiotic prophylaxis were found to be effectiveness in recurrence prevention (and the associated cost savings), the cost of the preparations themselves, and potential cost savings achieved by preventing antibiotic resistance.

The legal situation is complex because preparations made from the investigated plants (or plant components) may be marketed as either herbal medicinal products or dietary supplements. Unlike prescription drugs, dietary supplements do not require proof of efficacy, while herbal medicinal products do so only to a limited extent. For patients, very similar packaging often additionally complicates determining a preparation's product category. Herbal medicinal products are reimbursed by health insurance funds only in isolated cases, and dietary supplements are never reimbursed. This aspect is relevant from an ethical and social perspective because many patients would like to use herbal medicinal products to treat lower UTIs, but they have to pay for them out of pocket. For society, potentially reducing antibiotic use via herbal medicinal products is a highly relevant aspect. Since current guidelines recommend antibiotics for the long-term prevention of lower UTIs only in exceptional cases, said societal aspect primarily concerns the acute treatment of lower UTIs. However, no study data are available on the efficacy of herbal medicinal products in the acute care of lower UTIs in women with recurrent uncomplicated lower UTIs.

Further research is needed: High-quality studies providing detailed information on the investigated preparations' composition would allow making more definitive statements regarding the effectiveness and transferability of these conclusions to preparations available in Germany. If appropriately disseminated, this information might help affected patients navigate through the very nontransparent market of herbal medicinal products and dietary supplements. Studies proving effectiveness are also a prerequisite for approval as prescription-only drugs and hence for general reimbursability. This approval, in turn, would give all affected patients easy access to (effective) PPs.

Two currently ongoing studies (which both investigate cranberry preparations) might supply additional data relevant for the research question.

Conclusion in terms of addressing the concerns of those proposing the topic:

The preventive use of cranberry preparations may be a good option for women with uncomplicated recurrent lower UTIs because such use is associated with an indication of benefit for relapse prevention in comparison with placebo, and the S3 guideline recommends preventive use of antibiotics only in exceptional cases. Due to very limited data being available, it is impossible to assess whether the preventive use of other phytopreparations may be a good option. No data are available on the use of cranberry preparations or other phytopreparations in the acute treatment of symptomatic episodes experienced by women with uncomplicated recurrent lower UTIs.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/ht20-01.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [93] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 6 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 6: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** 3Section.1; Chapter 4
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2; Chapter 5
Ethical analysis (ETH)	**Ethical aspects** Section 3.3; Section 6.1
Patients and social aspects (SOC)	**Social aspects** Section 3.3 Section 6.2
Legal aspects (LEG)	**Legal aspects** Section 3.3; Section 6.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.3; Section 6.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1– Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to November Week 3 2020
- Ovid MEDLINE(R) Daily Update November 25, 2020

The following filters were adopted:

- RCT: Lefebvre [94] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	urinary tract infections/
2	((urinary* adj1 tract* adj1 infection*) or cystitis*).ti,ab.
3	or/1-2
4	exp embryophyta/
5	phytotherapy/
6	exp plant preparations/
7	fruit/
8	(herbal* or phytotherap* or (non* adj1 antibiotic*) or nonantibiotic*).ti,ab.
9	(arborvitae* or ash*2 or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* adj1 tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*).ti,ab.
10	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* adj1 anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* adj1 (dioica* or urens*)) or (uva* adj1 ursi*) or vaccinium*).ti,ab.
11	or/4-10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	(randomized or placebo or randomly or trial or groups).ab.
15	drug therapy.fs.
16	or/12-15
17	16 not (exp animals/ not humans.sh.)

#	Searches
18	cochrane database of systematic reviews.jn.
19	(search or medline or systematic review).tw.
20	meta analysis.pt.
21	or/18-20
22	or/17,21
23	and/3,11,22
24	23 not (comment or editorial).pt.
25	24 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to November 25, 2020
- Ovid MEDLINE(R) Epub Ahead of Print November 25, 2020

#	Searches
1	((urinary* and tract* and infection*) or cystitis*).ti,ab.
2	(herbal* or phytotherap* or (non* adj1 antibiotic*) or nonantibiotic*).ti,ab.
3	(arborvitae* or ash*2 or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* and tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*).ti,ab.
4	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* and anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* and (dioica* or urens*)) or (uva* and ursi*) or vaccinium*).ti,ab.
5	or/2-4
6	(clinical trial* or random* or placebo).ti,ab.
7	trial.ti.
8	(search or meta analysis or medline or systematic review).ti,ab.
9	or/6-8
10	and/1,5,9
11	10 not (comment or editorial).pt.
12	11 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 November 25

The following filters were adopted:

- RCT: Wong [95] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	*urinary tract infection/
2	urinary tract infections/
3	((urinary* adj1 tract* adj1 infection*) or cystitis*).ti,ab.
4	or/1-3
5	exp embryophyta/
6	exp beverage/
7	exp *plant medicinal product/
8	phytotherapy/
9	(herbal* or phytotherap* or (non* adj1 antibiotic*) or nonantibiotic*).ti,ab.
10	(arborvitae* or ash*2 or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* adj1 tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*).ti,ab.
11	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* adj1 anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* adj1 (dioica* or urens*)) or (uva* adj1 ursi*) or vaccinium*).ti,ab.
12	or/5-11
13	(random* or double-blind*).tw.
14	placebo*.mp.
15	or/13-14
16	(meta analysis or systematic review or medline).tw.
17	or/15-16
18	and/4,12,17
19	18 not medline.cr.
20	19 not (exp animal/ not exp human/)
21	20 not (conference abstract or conference review or editorial).pt.
22	21 and (english or german).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 11 of 12, November 2020
- Cochrane Database of Systematic Reviews: Issue 11 of 12, November 2020

#	Searches
1	[mh ^"urinary tract infections"]
2	((urinary* near/1 tract* near/1 infection*) or cystitis*):ti,ab
3	#1 or #2
4	[mh "embryophyta"]
5	[mh ^"phytotherapy"]
6	[mh "plant preparations"]
7	[mh ^"fruit"]
8	(herbal* or phytotherap* or (non* near/1 antibiotic*) or nonantibiotic*):ti,ab
9	(arborvitae* or ash* or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* near/1 tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*):ti,ab
10	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* near/1 anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* near/1 (dioica* or urens*)) or (uva* near/1 ursi*) or vaccinium*):ti,ab
11	#4 or #5 or #6 or #7 or #8 or #9 or #10
12	#3 and #11
13	#12 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
14	#13 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
15	#14 in Trials
16	#12 in Cochrane Reviews, Cochrane Protocols

4. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	"urinary tract infections"[mh]
2	(urinary* and tract* and infection*) or cystitis*
3	#2 OR #1
4	embryophyta[mhe]
5	phytotherapy[mh]
6	"plant preparations"[mhe]
7	fruit[mh]
8	herbal* or phytotherap* or "non antibiotic" or nonantibiotic*
9	arborvitae* or ash* or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* and tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*
10	arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* and anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* and (dioica* or urens*)) or (uva* and ursi*) or vaccinium*
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4
12	#11 AND #3

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(urinary tract infection OR cystitis) AND (herbal OR herb OR phytotherapy OR "non antibiotic" OR nonantibiotic OR cranberry OR uva ursi)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
((urinary tract infection*) OR cystitis) AND (herb* OR phytotherapy OR "non antibiotic" OR nonantibiotic* OR non-antibiotic* OR cranberry OR (uva ursi) OR uva-ursi)

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
herb* AND urinary tract infections OR phytotherapy AND urinary tract infections OR non antibiotic* AND urinary tract infections OR nonantibiotic* AND urinary tract infections OR cranberry AND urinary tract infections OR uva ursi AND urinary tract infections OR herb* AND cystitis OR phytotherapy AND cystitis OR non antibiotic* AND cystitis OR nonantibiotic* AND cystitis OR cranberry AND cystitis OR uva ursi AND cystitis

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 25, 2020

The following filters were adopted:

- Health economic evaluation: Glanville [96] – Emory University (Grady)

#	Searches
1	urinary tract infections/
2	((urinary* adj1 tract* adj1 infection*) or cystitis*).ti,ab.
3	or/1-2
4	exp embryophyta/
5	phytotherapy/
6	exp plant preparations/
7	fruit/
8	(herbal* or phytotherap* or (non* adj1 antibiotic*) or nonantibiotic*).ti,ab.

#	Searches
9	(arborvitae* or ash*2 or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* adj1 tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*).ti,ab.
10	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* adj1 anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* adj1 (dioica* or urens*)) or (uva* adj1 ursi*) or vaccinium*).ti,ab.
11	or/4-10
12	(economic$ or cost$).ti.
13	cost benefit analysis/
14	treatment outcome/ and ec.fs.
15	or/12-14
16	15 not ((animals/ not humans/) or letter.pt.)
17	and/3,11,16
18	17 not (comment or editorial).pt.
19	18 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 November 25

The following filters were adopted:

- Health economic evaluation: Glanville [96] – Embase G

#	Searches
1	*urinary tract infection/
2	urinary tract infections/
3	((urinary* adj1 tract* adj1 infection*) or cystitis*).ti,ab.
4	or/1-3
5	exp embryophyta/
6	exp beverage/
7	exp *plant medicinal product/
8	phytotherapy/
9	(herbal* or phytotherap* or (non* adj1 antibiotic*) or nonantibiotic*).ti,ab.

#	Searches
10	(arborvitae* or ash*2 or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* adj1 tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*).ti,ab.
11	(arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* adj1 anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* adj1 (dioica* or urens*)) or (uva* adj1 ursi*) or vaccinium*).ti,ab.
12	or/5-11
13	(cost adj effectiveness).ab.
14	(cost adj effectiveness).ti.
15	(life adj years).ab.
16	(life adj year).ab.
17	qaly.ab.
18	(cost or costs).ab. and controlled study/
19	(cost and costs).ab.
20	or/13-19
21	and/4,12,20
22	21 not medline.cr.
23	22 not (exp animal/ not exp human/)
24	23 not (Conference Abstract or Conference Review or Editorial).pt.
25	24 and (english or german).lg.

3. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	"urinary tract infections"[mh]
2	(urinary* and tract* and infection*) or cystitis*
3	#2 OR #1
4	embryophyta[mhe]
5	phytotherapy[mh]
6	"plant preparations"[mhe]
7	fruit[mh]
8	herbal* or phytotherap* or "non antibiotic" or nonantibiotic*

#	Searches
9	arborvitae* or ash* or bean* or bearberr* or bearsgrape* or birch* or birdweed* or blackcurrant* or burdock* or burdox* or cassis* or cedar* or centaury* or centauries* or chestnut* or coneflower* or couch* or cranberr* or cress* or dandelion* or echinacea* or goldenrod* or hawkweed* or horseflyweed* or horseradish* or horsetail* or indigo* or (java* and tea*) or juniper* or knotgrass* or knotweed* or lovage* or nettle* or orthosiphon* or parsley* or restharrow* or rosemar* or rupturewort* or sandalwood* or silverweed* or strawberr* or turmeric* or willowherb* or woundwort* or yerba*
10	arctostaphylos* or aesculus* or agropyron* or arctium* or (argentina* and anserina*) or armoracia* or baptisia* or betula* or centaurium* or curcuma* or elymus* or epilobium* or equisetum* or fragaria* or fraxinus* or herniaria* or hieracium* or ilex* or juniperus* or levisticum* or nasturtium* or ononis* or orthosiphon* or petroselinum* or pilosella* or polygonum* or potentilla* or ribes* or rosmarinus* or santalum* or solidago* or taraxacum* or thuja* or (urtica* and (dioica* or urens*)) or (uva* and ursi*) or vaccinium*
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4
12	#11 AND #3