22 July 2016
EMA/427414/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP scientific opinion to DG Internal Market, Industry, Entrerpreneurship and SMEs, Unit GROW D.4. "Health Technology & Cosmetics" on the principal mode of action of proanthocyanidins intended to be used for prevention and treatment of urinary tract infections - Art. 57 (1) of Regulation (EC) No 726/2004 of the European Parliament and of the Council*

Innovation Task Force (ITF) report

This scientific opinion refers exclusively to the case presented to the European Medicines Agency and does not prejudge any future evaluation by the Agency according to further scientific advancements.

This scientific opinion is not binding and is without prejudice to decisions taken by the European Commission or Member State Competent Authorities on matters falling within their own remits.

* *Article 57*
1. The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products. To this end, the Agency, acting particularly through its committees, shall undertake the following tasks…omissis…(j) upon request, providing technical and scientific support in order to improve cooperation between the Community, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation of medicinal products, .. omissis… (p) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products or the starting materials used in the manufacture of medicinal products

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Administrative information

Applicant:	None
Proposed product name (if relevant):	None
Company marketing the product (if relevant):	None
Substance:	proanthocyanidins
Proposed product:	Not specified
Intended use:	prevention and/or treatment of infections of the urinary tract
CHMP coordinator:	[redacted]
Agency coordinator:	[redacted]
Request dated:	13 May 2016

Terms of reference

The EC asked the Agency to consider the following question(s):

According to Article 1 (2) (a) of the Medical Devices Directive, in order to qualify as a medical device, an article cannot achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

Article 13 (1) (d) of the Medical Devices Directive authorises the European Commission, upon a request of a Member State, to take the necessary measures in order to decide whether a particular product or a product group falls within the definition of a medical device. Unit GROW D.4 is currently preparing such a decision on the qualification of the group of products whose principal intended action, depending on proanthocyanidins present in cranberry (*Vaccinium macrocarpon*), is to prevent or treat cystitis. The preliminary assessment, confirmed by the view of the large majority of Member States, is that the above product group should not be qualified as medical device as its principal mode of action is achieved by pharmacological, immunological or metabolic means.

However, as some Member States and some representatives of the industry express the opposite view, we would like to obtain your opinion on the mode of action of proanthocyanidins as specified in the attached Annex. Some of the products containing proanthocyanidins were claimed by the manufacturers to be qualified as medical devices while others were marketed as food supplement, medical device or consumer product. GROW D.4 has to assess the question whether these products can indeed be medical devices. The answer thereto depends mainly on the assessment of what is the principal mode of action.

1. Background information (edited from information submitted to the Agency)

The Agency is asked by the European Commission/ DG for Internal Market, Industry, Entrepreneurship and SMEs responsible for cosmetics and devices, for a scientific opinion pursuant to Article 57 (1) (p) of Regulation (EC) No 726/2004, for a scientific opinion on the principal mode of action of proanthocyanidins used in products which are intended by manufacturers for prevention and/or treatment of infections of the urinary tract.

This opinion is adopted in accordance with Article 57 (j) and (p) of Regulation (EC) No 726/2004.

2. Scientific information

2.1. Product profile (from information submitted to the Agency)

1. Name of the products/substance: Proanthocyanidins
2. Final product composition/components: Proanthocyanidins belong to a class of polyphenols found in a variety of plants. Of specific interest for this request are A2-type proanthocyanidins (PACs). At present we are only aware of products in which PACs are derived from cranberries (*Vaccinium macrocarpon*).
3. Intended medical use/intended action: Prevention and/or treatment of the urinary tract infections. Of specific interest is P-fimbriated *E. coli* but the mode of action linked to other pathogens relevant for the urinary tract infections should also be established.

2.2. Product presentation, composition and use

Examples of products containing proanthocyanidins: [redacted]®, [redacted]®, [redacted]®.

- [redacted]®: sachets (containing dry juice concentrate of *Vaccinium macrocarpon*) and capsules (containing dry juice concentrate and 'extract', not further specified) standardised on a daily dose of 36 mg proanthocyanidins (PAC A).

Claim: medical device, urinary tract infections, cystitis and prevention of relapse, cranberry contains PAC, which reduce the adhesion of bacteria on the inner surface of the urinary tract.

- [redacted] 30 capsules: capsules with 500 mg of '[redacted]™' with anti-adhesive properties, [redacted]™' not specified

Claim: [redacted] is a sanitary product indicated for the treatment and prevention of cystitis and urinary tract infections.

- [redacted]®: a food supplement constituted of 120 mg cranberry (*Vaccinium macrocarpon*) extracts (including 36 mg proanthocyanidins, not further specified) and 60 mg ascorbic acid.

Claim: 'Proanthocyanidins from [redacted]® may help to support defence against bacterial pathogens in the lower urinary tract'; 'Proanthocyanidins from [redacted]® cranberry product may help to reduce the P-fimbriated *E. coli* adhesion to uroepithelial cells'.

2.3. Mechanism of action *(from information submitted to the Agency)*

Three modes of action are considered:

- mechanical – coating of the surface of the bladder or of the bacteria (claimed by some manufacturers);
- pharmacological – antibiotic effect on the bacteria (claimed by other manufacturers and the most probable mode of action in the CHMP's opinion);
- immunological – interference with a receptor mediated mechanism of pathogenicity (possible mode of action).

2.4. Regulatory status *(Information submitted to the Agency)*

Products containing proanthocyanidins and/or cranberry as substance or preparation for use in urinary tract infections are currently marketed differently across the EU as food supplement, medical device or consumer product. A complete overview is not available.

While in most EU Member States products containing cranberry extracts (*Vaccinium macrocarpon*), whose claimed action to prevent and/or treat urinary tract infections is based on proanthocyanidins, are not qualified as medical devices, the European Commission received information that these products were qualified as medical devices in other EU Member States. EFSA rejected a number of health claims (Art. 13.5 or Art. 14 of Regulation (EC) No 1924/2006) linked to proanthocyanidins and cranberry-based food products in so far that no cause - effect relationship could be established between the consumption of PACs or cranberry products and various health claims (EFSA 2009-2014). The European Commission provided no information whether any of these products have been qualified as medicinal products. A complete list of products on EU Member State level is not available.

Legal definition

In accordance with Article 1 (2) of Directive 93/42/EEC:

(a) 'medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

— investigation, replacement or modification of the anatomy or of a physiological process,

— control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Guidance

According to Directive 93/42/EEC a medical device does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means.

However, there is no definition on the "principal intended action in or on the human body by pharmacological means" in the Directive; guidance is available in the MEDDEV published by the European Commission and the case law of the Court of Justice of the European Union (see below):

The Agency's Committee for Human Medicinal Products (CHMP) adopted the following opinions on mode of action:

- "Pharmacological means" is understood as a direct interaction between, or an indirect effect of, the molecules of the substance in question or its metabolites, and a constituent of the human body (including any of its parts, or an organism or other pathogens within or on the body) through any type of chemical binding which results in initiation, enhancement, mitigation or blockade of physiological or pathological characteristics. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.
- "Immunological" is understood as an action mediated or exerted (including e.g. stimulation, modulation, replacement) by immune-competent cells (e.g. lymphocytes, phagocytes, macrophages, dendritic cells) and/or by molecules involved in overall immunological response (e.g. toll-like receptors, complement factors, cytokines, antibodies).

  A mean of action can be considered "immunological" only when the immune response is the primary intended consequence of the administration of a substance. An immune response that is not the intended consequence of administration cannot be considered an immunological mode of action.

  Examples: vaccines, antigen, antivenoms and certain therapies which depend on an immunological means to target therapy.
- "Metabolic means" is understood as an action which involves an alteration, including stopping, starting or changing the rate, extent or nature of the chemical processes (whether normal or pathological) participating in, and available for, function of the human body (including any of its parts or an organism or a virus within or on the body).

  With regard to the concept of chemical process the binding between molecules which does not mediate, directly or indirectly, a response within or on the human body is considered a chemical, not a metabolic mode of action.

  The chemical mode of action should be reproducible in vitro in a closed not biological inert system. A typical chemical mode of action is the local pH modification or the sequestering action of a molecule.

MEDDEV 2.1/3 rev.3

"Pharmacological means is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect."

Court of Justice's Case C-308/11

http://eur-lex.europa.eu/legal-content/en/TXT/PDF/?uri=uriserv%3AOJ.C_.2012.331.01.0009.01.ENG

"Article 1(2)(b) of Directive 2001/83 must be interpreted as meaning that, for a substance to be regarded as exerting a 'pharmacological action' within the meaning of that provision, it is not necessary for there to be an interaction between the molecules of which it consists and a cellular

constituent of the user's body, as an interaction between that substance and any cellular constituent present within the user's body may be sufficient"

3. Scientific discussion (relevant to the question raised by the EC)

3.1. Data used for assessment

The assessment is based on data submitted by the European Commission and on publicly available literature references.

Not considered are data from technical files of specific products as these data are currently not available to the Agency.

3.2. Composition and quality aspects

The examples of products relevant with regard to the procedure (see above) do not contain proanthocyanidins from *Vaccinium macrocarpon* as single substance, substance group or purified procyanidinic fraction but as cranberry juice, powder, concentrate extract or 'cranberry active' mostly without specification.

Known constituents of cranberries are: polyphenols such as flavonoids (mostly derivatives of quercetin and myricetin), anthocyanins, catechins, proanthocyanidines, sugars, polysaccharides, vitamins like ascorbic acid, organic acids (e.g. quinic, malic, shikimic, citric and salicylic acid), iridoids, ursolic acid and derivatives (American Herbal Pharmacopoeia 2002, Guay 2009, Blumberg et al. 2013).

Procyanidins (polyflavan-3-ol oligomers) in cranberry have largely epicatechin units as tetramers and pentamers (Guay 2009).

Depending on further processing different amounts of fruit constituents are likely to be found in resulting preparations.

Proanthocyanidins including A-linked PACs

Proanthocyanidins (PAC or PACs) are a large group of colourless phenolic plant constituents that heated with acids deliver coloured anthocyanidins. Condensed proanthocyanidins are natural polymers with catechins (flavan-3-ols) as monomers and often divided into oligomeric and polymeric proanthocyanidins with the approximate threshold at a degree of polymerisation (DP) of about 8. Oligomers below DP 8 have an astringent taste and are soluble in ethanol. Mixtures of extractable proanthocyanidins of diverse DP are found in many plants, in foods and herbal medicinal products.

Also in cranberry flavan-3-ols are present as monomers, oligomers, and polymers. Oligomers and polymers represent 85% of the total flavan-3-ols on a weight basis. (-)-Epicatechin is the predominant constitutive unit in cranberry PACs (c-PAC). The building blocks of PACs are condensed either via a single C-C bond between C4 of the upper unit and C8 or C6 of the lower unit (**B-type PACs**) or with an additional ether-type bond between C2 of the upper unit and the hydroxyl group at C7 of the lower unit (**A-type PACs, A-PACs** or **PAC A**). PACs with at least one A-type linkage account for **51–91%** of total PACs in cranberry (Blumberg et al. 2013).

Qualitative and quantitative determination of PACs

The identification and quantitative determination of the heterogeneous constituents belonging to the family of PACs, including numerous stereoisomers for which commercial standards are lacking, is still problematic. Data obtained with global methods do not address this issue (Blumberg et al. 2013).

Considering the tremendous challenges to detect and standardise the complex group of proanthocyanidins as oligomeric or polymeric polyphenols analysed via different group parameters or as monomers (Krueger et al. 2013, Lin et al. 2014, Mikulic-Petkovsek et al. 2012, Turi et al. 2015) caution should be applied when comparing 'cranberry', 'cranberry bioactives', c-PAC or A-PAC which can -according to method/standards applied- in practice mean different qualities and quantities.

3.3. Relevant data regarding the mode of action in urinary tract infections (UTI) - pharmacodynamics

The assessment of a 'mode of action' is hampered by (1) the non-specific definition of the active substance in question and (2) the insufficient characterisation of possible active substances from most in vitro, in vivo and clinical studies available in the public domain. Thirdly, even if some quantification of tannins, total phenolics, total anthocyanidins, total cranberry proanthocyanidins, or A-linked proanthocyanidins is performed, very different results can be obtained according to methods/standards used. There is no official European Pharmacopoeia monograph or method for quantitative proanthocyanidin analysis in place.

A distinction between herbal substance/ preparation (the multicompound mixture as a whole considered as the active substance) and specific compounds or compound groups as active substance is necessary but in most studies and reviews not strictly made. A judgement on 'proanthocyanidins', or 'cranberry proanthocyanidins' or A- linked PACs is difficult as neither clearly defined nor tested as single fraction in many cases. Hence it is difficult to compare data for cranberry preparations and data for isolated compounds/ compound groups.

3.3.1. Antimicrobial activity of cranberry preparations and proanthocyanidins

UTIs are estimated to be caused to over 80% by uropathogenic *Escherichia coli*.

Bacteriostatic and bactericidal activity

In vitro:

> While older studies (e.g. Marwan & Nagel 1986, Lee et al. 2000, Puupponen-Pimiä et al. 2005) reported an inhibition of the growth of several bacterial strains in vitro by cranberry extracts some more recent studies concluded that cranberry products are non-bacteriostatic (Hidalgo et al. 2011, O'May & Tufenkji 2011). General there are doubts whether necessary concentrations can be reached in the human urine. Moreover there are reports that an inhibition of bacterial growth by cranberry extract requires a pH of 4.0 which is far below the pH achievable in human urine (Ahuja et al. 1998).

In vivo:

> No data available

Anti-adherence activities

In vitro:

Increasingly data support the hypothesis that cranberry /PAC hinder bacterial attachment to abiotic surfaces (Liu et al. 2006, Eydelnant & Tufenkji 2008) and to uroepithelial and kidney cells (Howell et al. 1998, Liu et al. 2008, Pinzon-Arango et al. 2009, Tufenkji et al. 2010), therefore preventing infection. However, a mechanistic understanding of the way in which cranberries influence bacterial behaviour is not consolidated. Cell culture methodologies have been used as an approach to studying the adherence/anti-adherence properties of *E. coli* strains in relation to UTI for cranberry and cranberry juice (di Martino et al. 2006, Howell et al. 2010, Ermel et al. 2012, Rafsanjany et al. 2013). Studies on cell cultures have also evidenced anti-adhesive capacity against uropathogenic P *E. coli* of urine samples collected after consumption of cranberry extracts (Howell et al. 2010, Lavigne et al. 2008, Stapleton et al. 2012). Cranberry extracts and some of their components (e.g., procyanidin A2) have also been tested for *E. coli* anti-adhesive activity (Ermel et al. 2012, Howell et al. 2005, Gupta et al. 2012), although it is unlikely that these structures will reach the uroepithelium in vivo - at least in relevant amounts.

Some publications suggest that the anti-adhesion response is partially dose dependent while more recent references (Rafsanjany et al. 2015) conclude that even PAC-depleted extracts exert antiadhesive properties.

Only recently a comparative study has been carried out testing among others cranberry extract (PAC-A rich), PAC dimers (A2 and B2), and simple phenols, bencoic-, pheylacetic- and phenypropionic acids as potential microbial-derived metabolites for their capacity to inhibit the adherence of uropathogenic *E. coli* ATCC®53503™ to T24 epithelial bladder cells. While some small entities showed anti-adhesive activity in a concentration-dependent manner from 100–500 μM, procyanidin A2, widely reported as an inhibitor of adherence on uroepithelium, was only statistically significant ($p < 0.05$) at 500 μM (51.3% inhibition). The cranberry extract showed no activity at all (de Llano et al. 2015).

Ex vivo/in vitro:

4 healthy volunteers received 600 mg cranberry extract (containing 1.24% PACs) daily for 7 days. The urine of these subjects was collected. Urine collected on the days 3 and 7 inhibited bacterial adhesion compared to a control urine sample (Rafsanjany et al. 2015).

In vivo:

No data available.

Influence on flagellation and motility of E. coli

In vitro:

PACs with A-type linkages were isolated which exhibited bacterial anti-adhesion activity against uropathogenic *E.coli* in vitro via inhibition of P-fimbriae synthesis and induction of a bacterial deformation both antibiotic susceptible and resistant bacteria (Lavigne et al. 2007).

Rafsanjany et al. (2015) found that neither a PAC containing extract nor a PAC depleted extract interacted with the formation of curli in the E. coli strain NU14.

Ex vivo/in vitro:

Similar results were obtained via ex-vivo measurements of human urine after cranberry phenolic extract (sugars removed) consumption – however, PACs were not determined (Lavigne et al. 2008).

Anti-biofilm properties

In vitro:

Some in vitro studies have found that cranberry A-type PACs have anti-biofilm properties against E*. coli* (e.g. Foo et al. 2000, Howell et al. 2005).

From other in vitro studies it seem other Gram-positive and Gram-negative bacteria were equally affected by a significant decrease in biofilm production when exposed to cranberry juice, extracts, or PACs (e.g. Yamanaka et al. 2004, 2007; Ulrey et al. 2014).

In vivo:

No data available.

3.3.2. Other potential activities

Adjuvant to antibiotics:

In vivo studies in a *G. mellonella* (wax moth larvae) model demonstrated a low dose of gentamicin with PACs prolonged survival in *P. aeruginosa*-infected worms significantly more than antibiotic or PACs alone. Thus cranberry PACs may be acting as antibiotic adjuvant for the action of gentamicin (Farha et al. 2013).

Anti-inflammatory effects:

Cranberry/PACs are supposed to reduce UTI-related symptoms by suppressing inflammatory cascades as an immunologic response to bacteria invasion. Anti-inflammatory activities get usually more attention in investigation of other potential effect and uses of cranberry and cranberry constituents such as cardiovascular, anticancer or periodontal effects (Neto et al. 2006, Blumberg et al. 2013).

Several in vitro studies suggest that cranberry constituents suppress the activation of macrophages and T cells exposed to relevant pro-inflammatory stimuli. Anthocyanins are reported having effects on microvascular endothelial cells and several factors involved in the inflammatory cellular response such as intercellular adhesion molecule 1 (ICAM-1) or nuclear factor kappa B (NF-κB). Different preparations and phenolics derived from cranberry are also reported to inhibit COX-2, TNF-α or production of LPS induced interleukins. Anti-inflammatory effects are often linked to flavonoids such as quercetin or triterpenes such as ursolic acid. Some in vivo data equally suggest influence on inflammatory parameters and response. (Neto et al. 2006, Blumberg et al. 2013)

3.3.3. Summary

The mechanisms implied in the preventive effects of cranberry/PACs against UTI are not completely established.

No human pharmacological data are available.

Highly preliminary ex vivo/in vitro data suggest that cranberry constituents or metabolites present in human urine inhibit bacterial adhesion to uroepithelial cell (i.e antiadhesive activity). This effect may be independent of the amount of PACs administered.

In vitro experiments do not consider absorption and metabolism of cranberry constituents (see below).

There is some evidence from in vitro tests that extracts with and without PACs as well as isolated PACs may have an influence on the formation of fimbriae of uropathogenic *E. coli*.

To a minor extent it is suggested, mostly from in vitro data, that cranberry constituents other than PAC or A-PAC could contribute to both antibacterial effects but also have ant-inflammatory activities.

3.4. Pharmacokinetics and metabolism of proanthocyanidins

In general, proanthocyanidins exhibit low oral bioavailability (< 10%) owing both to poor water solubility and extensive presystemic metabolism (Manach et al. 2005, Rafsanjany et al. 2015).

Few pharmacokinetics studies have been carried out on cranberry specific proanthocyanidins due to the structural complexities as well as the lack of commercial standards (Di Martino et al. 2006).

Ohnishi et al. (2006) investigated the excretion of monomeric anthocyanins in human urine after ingestion of 200 ml cranberry juice (containing 650.8 µg total anthocyanins) by 11 healthy volunteers. Six of 12 anthocyanins identified in cranberry were quantified in human urine. The urinary levels of anthocyanins reached a maximum between 3 and 6 h after ingestion, and the recovery of total anthocyanins in the urine over 24 h was estimated to be 5.0% of the amount consumed. Proanthocyanidins were not analysed.

After a single ingestion of cranberry syrup Iswaldi et al. (2013) identified free coumaroyl hexose (isomer 1 and 2), dihydroxybenzoic acid, caffeoyl glucose, dihydroferulic acid 4-O-β-d-glucuronide, methoxyquercetin 3-O-galactoside, scopoletin, myricetin and quercetin, together with other 23 phase-I and phase-II metabolites, including various isomers in human urine. The allocation of these metabolites to original phenols and polyphenols in the syrup was not possible.

Recently, a single-dose pharmacokinetic trial was conducted in 10 healthy adults ≥ 50y to evaluate the acute (24-h) absorption and excretion of flavonoids, phenolic acids and proanthocyanidins (PACs) from a cranberry juice cocktail (54% juice). PAC-A2 dimers could be quantified in the urine. However, the authors conclude that urinary PAC-A2 is unlikely reflective of the specific bioavailability of PAC-A2 from cranberry intake (McKay et al. 2015).

Reviews conclude that although dimers (procyanidin A2) have been detected in urine (Zampariello et al. 2012), cranberry PAC overall are minimally absorbed because of non-hydrolyzable bonds between monomeric subunits and a propensity to bind proteins by hydrogen bonding (Krueger et al. 2013). Because of poor absorption, >95 % of PAC in general remain in the intestinal lumen, the degree of procyanidin polymerization has a major impact on their fate in the body characterized by a poor absorption and a limited metabolism by the intestinal microflora as compared to monomeric catechin (Gonthier et al. 2003).

The presence of intact proanthocyanidins in human urines is very much doubted (Di Martino et al. 2006).

Summary on pharmacokinetics

There is evidence that intact A PACs from cranberry are poorly absorbed.

There are no data available demonstrating the presence of PACs with a degree of polymerisation of more than two in human urine.

4. Conclusion

4.1. Conclusions on PACs

- In vitro data have shown that cranberry PAC/A-PAC inhibits primarily P-fimbriated uropathogenic strains of *E. coli* from adhering to uroepithelial cells.
- The reduction in adhesion forces may be due to changes in bacterial morphology and/or genetically based decreases in P-fimbrial expression.
- Human pharmacological data are missing. Preliminary ex vivo human data support the antiadhesive theory.
- The bioavailability of PACs and A-PACs is not fully known. Oligomeric and polymeric PAC are usually not absorbed or to low extent only (< 10%). There are no reports confirming the presence of PACs in the urine.
- Due to the very limited bioavailability of PACs it can be assumed that the concentrations needed for a mechanical mode of action are likely not be reached in the bladder. Therefore a mechanical principal mode of action is highly unlikely.

4.2. Conclusions on herbal preparations from cranberry

- Products containing proanthocyanidins from *Vaccinium macrocarpon* are rarely marketed as containing a single substance or a substance group but rather as cranberry juice, powder, concentrate, extract or 'cranberry active' mostly without specification. As a consequence, these products contain a vast number of different substances. Therefore, this opinion includes as well the principal mode of action of herbal preparations from *Vaccinium macrocarpon* used in products which are intended by manufacturers for prevention and/or treatment of infections of the urinary tract.
- Cranberry preparations and certain cranberry constituents have shown in vitro bactericidal and bacteriostatic effects.
- PAC free extracts also exhibited in vitro antiadhesive effects.
- There is some general evidence mostly from in vitro data for other potential effects such as ant-inflammatory due to the presence of flavonoids and terpenic constituents which are likely present in products containing extracts.
- Both, free lower molecular phenolic metabolites and in particular phenolic acids have been found in human urine after consumption of cranberry.
- The presence of constituents in the urine exerting in vitro pharmacological activity suggests a pharmacological mode of action.

Although there are gaps in the scientific knowledge on the mode of action of PACs, the totality of data suggests that a mechanical mode of action of PACs is highly unlikely. Metabolites of PACs and other constituents of cranberry exhibit most probably a pharmacological activity.

The conclusion does not include an evaluation of clinical efficacy of products containing preparations and/or proanthocyanidins from *Vaccinium macrocarpon* which are intended by manufacturers for prevention and/or treatment of infections of the urinary tract.

5. CHMP opinion

The CHMP having considered:

- The information provided by the EC
- the definition of a 'medical device' (as per Article 1(2) of Directive 93/42/EEC)
- EC guidance document MEDDEV 2.1/3 rev.3
- Ruling of the Court of Justice of the European Union in Case C-308/11
- Scientific literature

is of the following opinion:

The totality of data suggests that a mechanical mode of action of PACs is highly unlikely. Metabolites of PACs and other constituents of cranberry exhibit most probably a pharmacological activity.

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EFSA 05 May 2014: Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006 https://www.efsa.europa.eu/en/efsajournal/pub/3656

EFSA 05 May 2014: Scientific Opinion on the substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006 https://www.efsa.europa.eu/en/efsajournal/pub/3657

EFSA 12 February 2013: Scientific Opinion on the substantiation of a health claim related to Monurelle® and reduction of bacterial colonisation of the urinary tract by the inhibition of the adhesion of P-fimbriated E.coli to uroepithelial cells pursuant to Article 13(5) of cranberry (*Vaccinium macrocarpon*) extract (including 36 mg proanthocyanidins) and 60 mg of ascorbic acid, is ... effect. https://www.efsa.europa.eu/en/efsajournal/pub/3082

EFSA 13 February 2009: Ocean Spray Cranberry Products® and urinary tract infection in women-Scientific substantiation of a health claim related to Ocean Spray Cranberry Products® and urinary tract infection in women pursuant to Article 14 of Regulation (EC) No 1924/2006 [1] https://www.efsa.europa.eu/en/efsajournal/pub/943

EFSA 21 December 2009: Scientific Opinion on the substantiation of a health claim related to a Uroval® and urinary tract infection pursuant to Article 14 of Regulation (EC) No 1924/2006 https://www.efsa.europa.eu/en/efsajournal/pub/1421

EFSA 26 July 2013: Scientific Opinion on the substantiation of a health claim related to proanthocyanidins in Urell® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated E. coli to uroepithelial cells pursuant to product containing cranberry (*Vaccinium macrocarpon*) juice powder standardised for proanthocyanidins (PAC) ... related to proanthocyanidins in cranberry and reduction of bacterial colonisation of the urinary tract by ... is

Urell®, a food supplement containing cranberry (*Vaccinium macrocarpon*) juice powder standardised … https://www.efsa.europa.eu/en/efsajournal/pub/3326

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