

# SAFETY AND EFFICACY OF CRANBERRY (*Vaccinium Macrocarpon*) DURING PREGNANCY AND LACTATION

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## ABSTRACT

### Background

There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbs used during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

### Objectives

To systematically review the literature for evidence on the use, safety and pharmacology of cranberry, focusing on issues pertaining to pregnancy and lactation.

### Methods

We searched 7 electronic databases and compiled data according to the grade of evidence found.

### Results

There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. Indirectly, there is good scientific evidence that cranberry may be of minimal risk, where a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of cranberry is unknown.

### Conclusions

Women experience urinary tract infections with greater frequency during pregnancy. Given the evidence to support the use of cranberry for urinary tract infections (UTIs) and its safety profile, cranberry supplementation as fruit or fruit juice may be a valuable therapeutic choice in the treatment of UTIs during pregnancy.

**Key words:** *Cranberry, vaccinium macrocarpon, pregnancy, lactation, breastfeeding, systematic review*

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American cranberry (*Vaccinium macrocarpon*) is one of the few fruits native to Eastern North America. It is also found in Northern Europe. Traditional medicinal use of cranberry fruit by Native Americans was primarily for the treatment of bladder and kidney ailments.<sup>1</sup> There has also been a relatively long history of scientific research on this herbal remedy, dating back to its

chemical characterization in the late 19<sup>th</sup> century.<sup>2</sup> Cranberry's principal therapeutic value today continues to be for the treatment and prevention of urinary tract infections.<sup>3</sup> It was originally thought that cranberry's biological activity was due to an acidifying effect on urine, however, this theory has been largely disproved.<sup>1</sup> The currently accepted mechanism of action in treating and

preventing urinary tract infections is through disabling *Escherichia coli*'s capacity to adhere to the urethra.<sup>2,4</sup> The fruit contains two compounds, fructose and a proanthocyanidin, that adhere to proteins on the fimbriae of *E. coli*, effectively inhibiting the bacteria from sticking to the epithelial cell lining of the urethra.<sup>2,4</sup> Without the ability to establish a strong foothold via adherence, the infection is either attenuated or prevented at the outset.

The pregnant woman, along with a number of other issues, has to deal with an increased frequency of urinary tract infections.<sup>5,6</sup> Given the recognised safety of cranberry juice and its efficacy in the treatment of urinary tract infections<sup>2,7</sup>, it is of no surprise that this therapy is widely used by pregnant women. A survey of 400 women from Norway found that cranberry fruit juice was the most commonly used herbal therapy during pregnancy.<sup>8</sup> The popular use of this herb during pregnancy calls for an in-depth understanding of its efficacy and potential for harm during pregnancy and lactation. We endeavoured to address these issues in a systematic review of the literature.

#### Synonyms/Common Names/Related Substances

American cranberry, arandano Americano, arandano trepador, cranberries, European cranberry, grosse moosbeere, kranbeere, canneberge, large cranberry, moosebeere, mossberry, ronce d'Amerique, small cranberry, trailing swamp cranberry, tsuru-kokemomo, *Vaccinium*, *Vaccinium macrocarpon*<sup>9</sup>

#### Constituents

Proanthocyanidins, triterpenoids, lectins, catechins, ascorbic acid, benzoic acid, quinic acid, oxalic acid, citric acid and malic acid<sup>10</sup>

#### Part Used

Fruit<sup>9</sup>

### METHODS

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provided information as to the safety, efficacy and pharmacology of cranberry in pregnancy and lactation. We searched the following databases

from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database and Natural Standard. The common and Latin names of the herb were used as the key words along with “pregnancy”, “lactation” and “breastfeeding”. In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in the final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm is rated as displayed in Table 2.

### RESULTS

#### Indications for Use

	Evidence Grade
Prevention of urinary tract infections <sup>11</sup>	A
Prevention of stomach ulcers <sup>12,13</sup>	E
Prevention of periodontal disease <sup>14-16</sup>	E
Influenza prevention <sup>17</sup>	E

#### Use and Safety during Pregnancy

	Level of evidence for potential harm
Commonly used without evidence of harm <sup>8,18</sup>	3a
Minimal risk (taken as food) <sup>19</sup>	5

A survey was conducted on 400 Norwegian postpartum women.<sup>8</sup> The authors reported that cranberry was one of the most commonly used herbs during pregnancy.<sup>8</sup> A herbal compendium reported that cranberry is of minimal risk during pregnancy when consumed in food quantities.<sup>19</sup> There are no clinical studies in the evidence-based medicine literature of cranberry being either safe or contraindicated during pregnancy.

#### Use and Safety during Lactation

	Level of evidence for potential harm
Unknown	6

There are no reports in the evidence-based medicine literature of cranberry being either safe or contraindicated during lactation.

### Toxicity and Adverse Effects

Cranberries have been consumed as a food throughout recorded history and have proven safe as a food item. This track record of safety does not necessarily imply, however, that the fruit (processed or not) is entirely safe in all populations or at high levels of consumption. One possible area of concern is patients at risk of kidney stones. In a study of healthy volunteers consuming cranberry tablets for one week at the manufacturer's recommended dose, urinary oxalates were found to have increased significantly.<sup>20</sup> While consumption of up to 4L/day of cranberry juice has been shown to be non-toxic in healthy individuals<sup>21</sup>, people with nephrolithiasis may be at increased risk for stone formation if consuming large amounts of cranberries or cranberry juice. In infants and young children, gastrointestinal distress, including diarrhea, has been reported when consuming more than 3L/day of cranberry juice.<sup>22-24</sup>

### Pharmacology

The proanthocyanidins present in cranberry fruit interfere with bacterial adherence to the urinary tract epithelial cells.<sup>25-33</sup> The fructose in cranberries has also been shown to contribute to the antibacterial activity of cranberry.<sup>31,34,35</sup> In the case of *Escherichia coli* (*E. coli*), the cause of most urinary tract infections, proanthocyanidins have been shown to wrap around these bacteria and prevent their adherence to the urinary tract wall.<sup>13,34,36,37</sup> Cranberry juice cocktail was shown to inhibit adherence in 77 clinical isolates of *Escherichia coli* obtained from patients with diagnosed urinary tract infections.<sup>36</sup> It has been demonstrated, however, that cranberry does not appear to be able to dislodge bacteria that have already adhered to the urinary tract epithelial cells.<sup>38</sup>

Cranberry juice has antibacterial activity against *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus mirabilis*.<sup>30,34,36</sup> Cranberry has been shown to have antiviral action against the poliovirus type 1<sup>39</sup>; and has been found to prevent the adherence of *Helicobacter pylori* (*H. pylori*) in

the stomach.<sup>12,13</sup> Cranberry may also prevent adhesion of plaque bacteria that cause periodontal disease.<sup>14-16</sup> Recent findings indicate that cranberry may even reduce adhesion and infectivity of the influenza virus.<sup>17</sup> Cranberry has significant levels of antioxidant and has demonstrated anticarcinogenic activity.<sup>40,41</sup>

### Drug Interactions

Anecdotal reports of interaction with warfarin have been made<sup>42-44</sup>, however, in a clinical study of 14 healthy individuals, no alteration of CYP2C9, the enzyme responsible for metabolizing warfarin, was evident.<sup>45</sup> One laboratory study indicates that cranberry juice may inhibit enteric CYP3A4<sup>46</sup>, yet, a clinical study found no evidence of altered levels of cyclosporine, a CYP3A4 substrate, due to consumption of cranberry juice.<sup>47</sup>

## DISCUSSION

There is extensive research on the constituents and potential therapeutic properties of cranberry fruit and juice. The predominant theme of the research to date, both clinical and preclinical, involves the exploration of cranberry fruit's ability to reduce the risk of infection, particularly of the urinary tract, by a process of directly inhibiting a pathogen's ability for tissue and host cell adherence. Evidence suggests that not only is this possible for bacteria, but also for viruses as well.

There is very strong evidence supporting the use of cranberry in the prevention of urinary tract infections. A Cochrane database systematic review investigating the use of cranberry for the prevention of urinary tract infections, concluded that cranberry juice may effectively prevent the frequency of urinary tract infections.<sup>11</sup> While evidence regarding other uses of this fruit is nowhere near as rigorous, there are some promising *in vitro* evidence related to oral hygiene, *H. pylori* induced stomach ulceration, and even possibly in the prevention of influenza.

There is no direct evidence of safety or harm to the mother or fetus as a result of consuming cranberry during pregnancy. As reported above, a survey of 400 pregnant women did not uncover any adverse events when cranberry was regularly consumed. In lactation, the safety or harm of

cranberry is unknown. Its common usage, low toxicity and the fact that cranberries are eaten as a food, however, does support the hypothesis of safety in pregnancy and lactation when consumed in food amounts. At higher dosages, however, the safety or harm cannot be confirmed without further high quality clinical studies.

In the situation where a woman is predisposed to nephrolithiasis, however, caution is warranted in the consumption of foods containing high amounts of oxalic acid, cranberries included. Increased risks to the fetus either from radiographic diagnosis, treatment and even stone passage make the formation of kidney stones even more problematic and potentially risky for the

pregnant woman.<sup>48</sup> It should be noted, however, that pregnant women are not generally at increased risk for stone formation.<sup>49</sup>

Overall, cranberry appears to be a useful therapeutic agent for the prevention of urinary tract infections in women who are either pregnant or breastfeeding. Promising evidence regarding other anti-infective properties of cranberry need to be further pursued, including improved oral hygiene, stomach ulceration and the prevention of influenza. It is encouraging that there is a nutritious natural health product available that, in most cases, may safely prevent a common and debilitating complaint in pregnant woman.

**TABLE 1** Levels of Evidence for Efficacy

<b>GRADE</b>	<b>LEVEL OF EVIDENCE</b>
A	<b>VERY STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	<b>STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	<b>GOOD SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	<b>WEAK SCIENTIFIC EVIDENCE</b> Statistically significant evidence of benefit from one or more cohort studies OR case control studies.
D	<b>VERY WEAK SCIENTIFIC EVIDENCE</b> Evidence from case series OR case reports.
E	<b>INDIRECT EVIDENCE</b> Expert opinion OR laboratory studies.
F	<b>HISTORICAL OR TRADITIONAL EVIDENCE</b> Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.

**TABLE 2** Levels of Evidence for Harm

<b>LEVEL</b>	<b>EVIDENCE</b>
1	<b>STRONG SCIENTIFIC EVIDENCE</b> Statistically significant evidence from one or more systematic reviews or RCTs.
2	<b>ACCEPTABLE SCIENTIFIC EVIDENCE</b> Statistically significant evidence from one or more well designed cohort studies OR case control studies.
3a	<b>WEAK SCIENTIFIC EVIDENCE</b> Evidence from one or more case series.
3b	<b>VERY WEAK SCIENTIFIC EVIDENCE</b> Evidence based on case reports.
4	<b>INDIRECT SCIENTIFIC EVIDENCE</b> Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
5	<b>THEORETICAL EVIDENCE</b> Evidence based on scientific theory OR expert opinion.
6	<b>UNKNOWN</b> No available information.

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