



# Painful Bladder Syndrome/Interstitial Cystitis: Current Concepts and Role of Nutraceuticals

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Chronic pelvic pain syndrome (CPPS) affects approximately 1 of 60 adults in the United States and is associated with significant disability and poor quality of life. Painful bladder syndrome/interstitial cystitis (PBS/IC) has emerged as a major cause of CPPS along with irritable bowel syndrome (IBS), endometriosis, and chronic prostatitis (CP). PBS/IC is a heterogeneous clinical syndrome occurring mostly in women, with some evidence suggesting it may have similar features to CP. PBS/IC is characterized by severe pelvic and perineal pain, as well as urgency and frequency of urination in the absence of a bacterial infection or bladder cancer. PBS/IC is associated with other comorbid conditions, such as allergies/asthma and fibromyalgia, that are worsened by stress. Neurogenic inflammation leading to neuropathic pain has been increasingly implicated in PBS/IC. There are no curative treatments. Management of PBS/IC should address younger, newly diagnosed patients. This could be accomplished with unique nutraceutical formulations containing natural bladder lining rebuilding and antiinflammatory molecules, such as chondroitin sulfate, sodium hyaluronate, and quercetin.

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One of the most challenging presentations to a number of medical specialties is chronic pelvic pain (CPP) that affects more than 1 of 60 individuals in the United States.<sup>1</sup> CPP includes endometriosis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), as well as painful bladder syndrome/interstitial cystitis (PBS/IC), and chronic prostatitis (CP).

PBS/IC is a painful bladder disorder of unknown etiology, occurring mostly in women,<sup>2,3</sup> for which there is no effective therapy.<sup>4</sup> It is a diagnosis of exclusion characterized by >9 months of suprapubic or pelvic pain, as well as urgency and frequency of urination with nocturia in the absence of a urinary tract infection (UTI).<sup>2</sup> Pain of PBS/IC is commonly experienced suprapubically or in the lower back, but may also involve the perineum and vulva (vulvodynia, vulvar vestibulitis). Symptoms suggestive of a UTI is the most common reason these patients visit a clinician since all (back pain, dysuria, frequency) but one symptom (hematuria)<sup>5</sup> are

present. Clinical characteristics suggest that PBS/IC is a *heterogeneous syndrome*,<sup>6,7</sup> the symptoms disability of which can be elicited with the validated one page "O'Leary-Sant" Symptom and Problem Index.<sup>8</sup>

Most women with PBS/IC experience dyspareunia and exacerbation of their symptoms with sexual intercourse<sup>9</sup> and ovulation<sup>7,10</sup>; PBS/IC certainly impacts adversely on female sexual function.<sup>11</sup> This effect could involve bladder mast cells that express estrogen receptors,<sup>12,13</sup> especially since estradiol augments PBS/IC bladder mast cell secretion induced by acetylcholine and substance P (SP).<sup>14</sup>

PBS/IC patients suffer from other comorbid diseases,<sup>7,11,15,16</sup> with some component of neurogenic inflammation.<sup>17</sup> These include allergies/asthma (45-60%), atopic dermatitis (40%), IBS (40%), endometriosis (30%),<sup>18</sup> vulvodynia (30%),<sup>19</sup> and fibromyalgia (25%).<sup>20</sup> Inflammatory bowel disease, Sjögren's syndrome, chronic fatigue syndrome, and multiple chemical sensitivities are less frequent.

Urgency and frequency of urination is less frequent in men with PBS/IC,<sup>21,22</sup> who often present with Type III male chronic pain syndrome, previously known as "prostatodynia," "abacterial prostatitis," or CP. PBS/IC and CP may be similar disorders with pelvic organ manifestations,<sup>21-23</sup> except that patients with CP experience perineal discomfort, as well as penile, perirectal, testicular (orchalgia), or scrotal (scrotodynia) pain.<sup>21,22</sup>

The prevalence of PBS/IC had been estimated as 55 per

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100,000<sup>24</sup> or 45 per 100,000<sup>25</sup> using the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria,<sup>2</sup> but has been reported to be 190 per 100,000 women in a managed care practice in the United States (without the consensus IC exclusion criteria cystoscopy with hydrodistention).<sup>25</sup> Most PBS/IC patients are Caucasian women with a median age of 43 years.<sup>26</sup> PBS/IC can occur in adolescents<sup>27,28</sup> and children.<sup>28,29</sup> There are a number of families with members in which the prevalence of PBS/IC in first-degree relatives was 17 times higher than in the general population.<sup>30</sup> Recent family linkage studies showed a strong association of PBS/IC with panic disorder.<sup>31</sup>

## Diagnosis

Currently, no specific markers are available for PBS/IC diagnosis that continues to be based on history and clinical features in the absence of other well-defined diseases.

Histamine metabolites,<sup>32</sup> the unique mast cell protease tryptase,<sup>33</sup> and IL-6<sup>34</sup> were increased in 24-hour urine of PBS/IC patients who met NIDDK criteria, but more so only in newly diagnosed PBS/IC patients.<sup>34,35</sup> An antiproliferative factor (APF) was increased in the urine and could distinguish PBS/IC from other urologic disorders.<sup>36</sup> APF was identified as a frizzled-8 sialoglycopeptide,<sup>37</sup> but no commercial assay is available yet.

The NIDDK criteria<sup>38</sup> include cystoscopy and “hydrodistention under general or spinal anesthesia” during which urothelial petechiae (glomerulations) may be observed. However, cystoscopy may be not necessary except when there is persistent hematuria (in which case pelvic CT should also be performed). “Classic” PBS/IC with Hunner’s ulcers is present in about 10% of patients. Biopsy may be necessary to exclude neoplasms and eosinophilic or tuberculous cystitis.

Intravesical administration of concentrated KCl has been proposed for diagnosis,<sup>39</sup> due to the pain it can elicit through depolarization of sensory nerves if the protective bladder glycosaminoglycan (GAG) layer is damaged. This test has low sensitivity and specificity (75%).

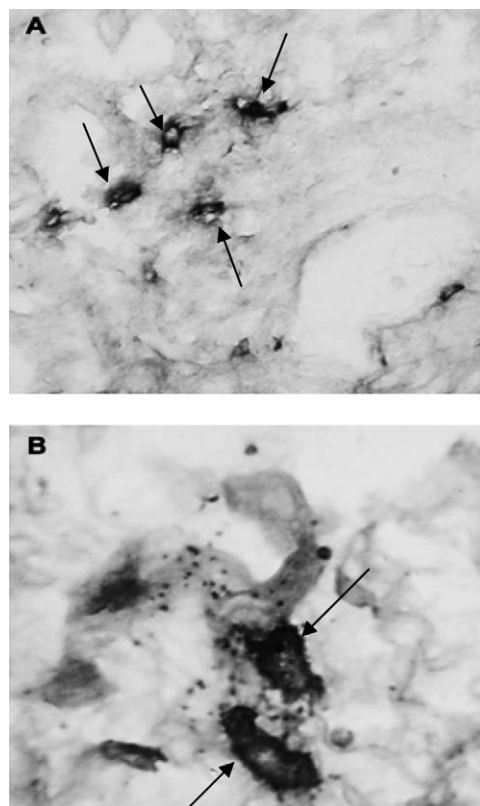
## Pathogenetic Mechanisms

PBS/IC patients report a history of UTIs, but no infection has been documented by culture.<sup>40,41</sup>

PBS/IC may involve some damage to the bladder GAG layer, which could induce urothelial inflammation/irritation.<sup>2,42,43</sup> The GAG is made of chondroitin sulfate (CS) and sodium hyaluronate (SH),<sup>7</sup> both of which<sup>44,45</sup> have been reported to be increased in the urine of PBS/IC. However, this increase could be due to increased synthesis without indicating any defect, since other studies have shown that the urothelium is intact.<sup>46</sup>

PBS/IC is associated with variable bladder inflammation,<sup>47-49</sup> but the degree of bladder inflammation did not correlate with the severity of cystoscopic findings.<sup>50</sup>

A main pathologic finding is the increased number of activated mast cells (Fig. 1) (for reviews see refs. 7 and 51). Classic PBS/IC has more mast cells in the detrusor, than

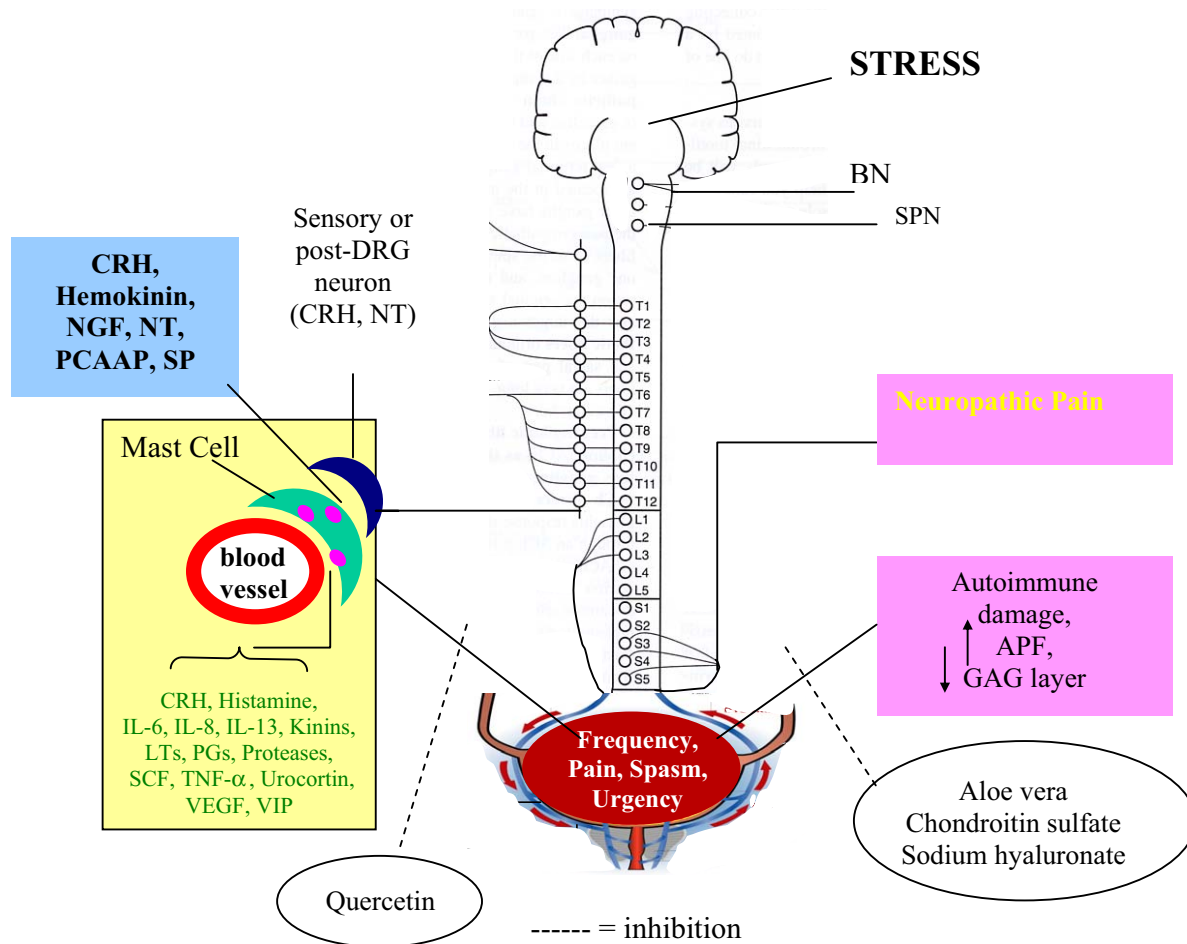


**Figure 1** Mast cells (arrows) in bladder biopsy from a female patient with severe PBS/IC stained immunohistochemically with anti-tryptase antibodies. (A) Mast cells closely associated with blood vessels; (B) two degranulated mast cells in the center of the panel. Magnification (A)  $\times 400$ ; (B)  $\times 1000$ .

common PBS/IC.<sup>52</sup> Bladder mastocytosis in PBS/IC could be due either to nerve growth factor (NGF)<sup>53</sup> or to the chemokine RANTES.<sup>54</sup> Results from the Interstitial Cystitis Database Study indicated that the only bladder pathological feature of PBS/IC that correlated with symptoms (nocturia)<sup>55</sup> was the high number of tryptase-positive bladder mast cells. Tryptase induces hyperexcitability of submucosal neurons, while histamine directly stimulates SP and calcitonin gene-related peptide-containing neurons.<sup>17,56</sup> Tryptase secreted from activated mast cells could stimulate protease activated receptors leading to widespread inflammation and neuronal hyperexcitability.<sup>17</sup>

Mast cells are critical for allergic and late phase reactions during which they release multiple mediators that are also been implicated in innate immunity,<sup>57</sup> autoimmunity,<sup>58</sup> and neuroinflammatory disorders.<sup>17</sup>

Bacterial or viral superantigens,<sup>59</sup> antibody light chains,<sup>60</sup> aggregated IgG<sup>59</sup> and anaphylatoxins,<sup>61</sup> as well as neuropeptides, such as SP and neurotensin can activate mast cells.<sup>17,62,63</sup> NGF<sup>64</sup> and stem cell factor, both of which are increased in PBS/IC bladders,<sup>53,65,66</sup> can also induce mast cell activation.<sup>67</sup> Mast cell mediators include the prestored histamine, kinins, and proteases, such as chymase and tryptase, as well as cytokines, leukotrienes, prostaglandins, and vascular endothelial growth factor (VEGF).<sup>17</sup> Bladder mast cells in PBS/IC may involve selective release of mediators,<sup>13</sup> such as



**Figure 2** Schematic representation of bladder neurogenic inflammation. CRH or related peptides from the pontine Barrington nucleus, acting through the spinal parasympathetic nucleus (SPN) that innervates the bladder or secreted in the bladder by sensory or postganglionic nerves, activate mast cells to release vasoactive, proinflammatory, and neurosensitizing molecules propagating a pathologic loop. BN, Barrington nucleus; DRG, dorsal root ganglion; IL-6, interleukin-6; LTs, leukotrienes; NGF, nerve growth factor; NT, neurotensin; APF, antiproliferative factor; PCAAP, pituitary cyclic AMP activating peptide; PGs, prostaglandins; SP, substance P; SPN, spinal parasympathetic nucleus; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide. (Color version of figure is available online.)

serotonin<sup>68</sup> and eicosanoids.<sup>69</sup> In particular, human mast cells could be activated by the cytokine IL-1 to secrete IL-6<sup>70</sup> and by corticotropin releasing hormone (CRH) to induce VEGF.<sup>71</sup> One isoform of VEGF released from mast cells is particularly vasodilatory<sup>72</sup> and could possibly contribute to glomerulations in which angiogenic growth factors are over-expressed.<sup>73</sup> Urine tryptase is increased in PBS/IC<sup>33</sup> and can cause microvascular leakage,<sup>74</sup> as can chymase.<sup>75</sup>

Functional neuroimmune networks in the bladder could participate in both bladder inflammation and neuronal hyperreactivity in PBS/IC<sup>56</sup> (Fig. 1). Mast cells are located perivascularly in close proximity to nerve endings,<sup>13,76,77</sup> especially those containing SP,<sup>76,78</sup> which can activate mast cells.<sup>79</sup> Intravesical administration of SP induced bladder inflammation<sup>80</sup> through NK-1 receptors.<sup>81</sup> SP was increased in bladder biopsies of patients with PBS/IC.<sup>82</sup> The involvement of the nervous system is supported by evidence that antidromic stimulation of the lumbosacral dorsal roots induced vascular permeability in the rat urinary bladder<sup>83</sup> and bladder

inflammation was induced by CNS infection by pseudorabies virus that could not develop in mast cell-depleted mice.<sup>84</sup>

## Effect of Stress

Acute stress can precipitate or aggravate PBS/IC symptoms<sup>7,85-87</sup> and panic disorder was associated with PBS/IC,<sup>88</sup> possibly through mast cells.<sup>88,89</sup> Acute stress led to bladder mast cell activation.<sup>85,90</sup> and urothelial cell vacuolation, reminiscent of the histopathological changes in PBS/IC.<sup>86,91</sup> Acute restraint stress also increased urine histamine and IL-6 in rats.<sup>92</sup>

In addition to hypothalamic CRH,<sup>93</sup> it is also expressed in the spinal cord, dorsal root ganglia (DRG), sympathetic ganglia,<sup>94</sup> and skin,<sup>95</sup> where it may have proinflammatory actions,<sup>93,96</sup> through activation of mast cells<sup>97,98</sup> (Fig. 2). CRH administration to humans causes peripheral vasodilation and flushing, suggestive of mast cell activation, especially in women, and is mediated through mast cells.<sup>99,100</sup> Human

Table 1 Potential Nutraceuticals for PBS/IC

Ingredients/Trade Name	Dose Regimen*	Class	Adverse Effects	Companies
<b>Oral</b>				
Aloe vera (whole leaf)	600 mg each bid	Polysasscharide	N/A	desertharvest.com 1-800-222-3901
GS/CS/SH/Quercetin <sup>†</sup> (CystoProtek <sup>®</sup> )	260/300/40 mg each bid	Proteoglycans/flavonoid	N/A <sup>‡</sup>	algonot.com 1-800-Algonot
Calcium glycerophosphate (Prelief)		Antacid	N/A	prelief.com 1-800-994-4711
Quercetin <sup>†</sup>	300 mg bid	Flavonoid	N/A	nutricology.com 1-510-487-8526
Quercetin/bromelain/papain/ cranberry powder/black cohosh/skullcap/wood betony/passionflower/valerian (CystaQ, unknown amounts)	540 mg bid	N/A	Unknown	cystaq.com 1-877-284-3976
<b>Local (external)</b>				
Aloe + lidocaine HCl gel (Solarcaine)	10% aloe + 0.5% lidocaine	Local anesthetic	N/A	1-908-298-4000

CS, chondroitin sulfate; GS, glucosamine sulfate; N/A, not applicable; SH, sodium hyaluronate; bid, 2 times per day.

\*Maximum daily recommended dose.

<sup>†</sup>Preferably together.

<sup>‡</sup>May worsen diarrhea associated with irritable bowel syndrome.

mast cells also secrete CRH<sup>101</sup> and express CRH-R isoforms,<sup>98</sup> suggesting autocrine effects.

The only animal model for PBS/IC is a feline bladder condition<sup>102</sup> with many similar clinical and pathological features, including increased bladder mast cells.<sup>103</sup> Urinary bladders of such cats were also reported to have increased high affinity binding sites for SP.<sup>104</sup> A mouse with autoimmune cystitis was developed and was characterized by an increased number of bladder mast cells.<sup>105</sup> Intravesical administration in rodents of ovalbumin in sensitized rats,<sup>106</sup> lipopolysaccharide, or SP could induce bladder inflammation.<sup>80,107</sup> Such “models” showed that mast cells are required for bladder damage or inflammatory mediator release.<sup>85,108</sup>

## Treatment

There is no curative therapy for PBS/IC.<sup>4,4,109-111</sup> The National Institutes of Health (NIH) has funded a Research Network for multicenter clinical trials,<sup>112</sup> but all studies have so far turned out negative. The most common interventions for PBS/IC have been bladder hydrodistention, intravesical heparin, and oral amitriptyline.<sup>110</sup> Pelvic floor muscle physiotherapy has proven helpful in many patients.<sup>113</sup>

## Diet

Precipitating factors for PBS/IC include foods or beverages such as the ones that also trigger migraines (e.g., beer, cheese, monosodium glutamate, red wine, spices). There is widespread popular belief that urine acidity is associated with or worsens PBS/IC symptoms; hence, a dietary supplement con-

taining calcium glycerophosphate (Prelief) is widely used to reduce acidity. However, a prospective, double-blind, randomized cross-over study evaluating urine acidity (pH) showed no statistical difference in pain sensation between urine at physiologic acidity (pH 5.0) or urine with less acidity (pH 7.5) in 26 women with PBS/IC.<sup>114</sup>

## Replenishing the GAG Layer

Pentosan polysulfate (PPS), a synthetic polysaccharide originally synthesized as a heparin substitute, has been marketed under the Orphan Disease Act for “replenishing” the GAG layer. Early clinical trials showed that the response to PPS (300 mg/day for 3 years) was twice that of placebo, with regard to pain, but with no appreciable decrease in nocturia.<sup>2,4</sup> A recent NIH-sponsored multicenter double-blind, randomized, placebo-controlled 3-month clinical trial using 300 mg/day showed no effect.<sup>112</sup> Adverse effects to PPS include hair loss and possible bleeding complications.<sup>115</sup>

GAG is made up of CS and SH. The total GAG to sulfated GAG ratio and SH levels were increased in the urine of PBS/IC patients.<sup>45,116</sup> SH promoted urothelial healing in acid-induced cystitis<sup>117</sup> and inhibited stress-induced bladder mast cell inflammatory mediator release in rats.<sup>92</sup> As a result, intravesical SH was used (0.04% weekly for 4 weeks) and resulted a noticeable benefit in 50-70% of patients, which decreased after 20 weeks.<sup>48,118</sup> However, a double-blind, randomized, placebo-controlled clinical trial using 10 times higher (0.4%) SH failed to show any benefit (ICA; e-mail: icanews@ichelp.org). Combining SH and CS may provide additional benefit<sup>109</sup> (Table 1).

**Table 2** Characteristics of Olive Kernel Oil

- Low acidity and special filtration from Crete
- Provides greater solubility and absorption of chondroitin sulfate and quercetin
- Unsaturated fatty acids provide fluidity of biological membranes
- Antioxidants protect against peroxidation and other free radicals
- Polyphenols have antiinflammatory actions
- Contains a natural cyclooxygenase inhibitor
- Helps heal damaged mucosal surfaces

## Reducing Bladder Inflammation

No approach has attempted to address the bladder inflammation in PBS/IC. Flavonoids are naturally occurring molecules, rich in green plants and seeds, with potent antioxidant, cytoprotective, and antiinflammatory properties.<sup>119</sup> Quercetin is a naturally occurring flavonoid that blocks mast cell secretion and inflammation.<sup>119</sup> It has also been shown to inhibit bladder neurogenic inflammation (Fig. 2). Quercetin has been reported to be particularly potent in inhibiting the release of proinflammatory molecules from human mast cells.<sup>120</sup> The combination of quercetin with CS is additionally unique because CS blocks mast cell activation,<sup>121</sup> while quercetin blocks mast cell secretion and the two have synergistic action.<sup>122</sup> A pilot retrospective study using CystoProtek<sup>®</sup>, a formulation containing quercetin together with glucosamine sulfate (GS), CS, and SH for 6 months in 37 patients reduced PBS/IC symptoms by 55% ( $P < 0.01$ ).<sup>123</sup> This formulation

combines quercetin with CS and SH in olive kernel oil (OKO), which increases absorption of CS and quercetin.<sup>122</sup> This is critical because CS is a very large and negatively charged molecule, which results in <10% absorption in powder form<sup>122</sup>; quercetin is very lipophilic and does not dissolve in water. OKO not only uniquely increases absorption, but it provides additional useful properties that include antiinflammatory actions<sup>124,125</sup> as well as healing actions on mucosal surfaces<sup>126</sup> (Table 2). Moreover, olive oil used in the “Mediterranean diet” is well known to be associated with a significant reduction in total mortality.<sup>127</sup>

Another open label trial of 22 patients (5 men and 17 women) with PBS/IC used CystaQ, a quercetin (500 mg/day)-containing product of an undisclosed formulation twice per day for 1 month with about 40% improvement.<sup>128</sup>

The lack of disclosure purity, source, and certification of manufacturing facilities in this and other preparations is of particular concern. For instance, the most common quercetin source is from fava beans, which could cause hemolytic anemia in about 15% people of Mediterranean extraction that lack the enzyme G<sub>6</sub>PD. Most CS unfortunately is imported from cow trachea even though it is banned in Europe for fear of mad cow disease. CystoProtek<sup>®</sup> contains CS from shark cartilage and quercetin from the Saphora plant to avoid these problems (Table 3); moreover, it is produced by a Good Manufacturing Practices Certified Facility (Tischon Corp, Westbury, NY).

## Other Approaches

Downregulation of sensory nerve activation is important because it addresses pain. Arginine was used in a pilot study of

**Table 3** Comparison of Some Nutraceuticals Used for PBS/IC

Ingredients	Benefits	CystoProtek <sup>®*</sup>	Quercetin	CystaQ <sup>*,†</sup>
Glucosamine sulfate	Mucosal GAG layer building block	260 mg	None	None
Chondroitin sulfate <sup>‡</sup>	Mucosal GAG layer component, mast cell inhibitor	300 mg	None	None
Hyaluronate sodium	Mucosal GAG layer component	40 mg	None	None
Quercetin dihydrate <sup>§</sup>	Mast cell inhibitor, antioxidant, antiinflammatory	300 mg	300 mg	540 mg
Olive kernel oil	Antioxidant, Cytoprotective, Antiinflammatory, <sup>§</sup> increases absorption of active ingredients	900 mg	None	None
Manufacturer		Algonot, LLC 1-800-Algonot algonot.com	NutriCology, Inc 510-487-8526 nutricology.com	Farr Labs, LLC 1-877-284-3976 cystaq.com

\*Per minimum daily recommended dose (2 capsules).

†Proprietary formula—amounts and sources unknown.

‡From shark cartilage to avoid the most common source of cow trachea imported from Europe, which may be associated with spongiform encephalopathy (“Mad Cow Disease”).

§From Saphora plant to avoid common fava bean source that may cause hemolytic anemia in G<sub>6</sub>PD-deficient individuals of Mediterranean origin.

PBS/IC patients with a reported global improvement of 48% compared to 21% for control,<sup>129</sup> but a subsequent double-blind, randomized placebo-controlled cross-over study of 16 patients showed no benefit.<sup>130</sup>

Dry aloe leaf has also been used for presumed antiinflammatory properties.<sup>131</sup> A small prospective study using 900 mg/day showed some benefit.<sup>132</sup> This action may possibly be related to its reported ability to inhibit mast cell activation.<sup>133</sup>

## Reducing Peripheral Neural Activation

Vulvodynia and vulvar vestibulitis can occur in about 30% of women with PBS/IC. Local sensitivity/pain may be reduced with topical over-the-counter products containing aloe and lidocaine, such as Solarcaine®, commonly used for sunburns (Table 1).

## Conclusion

Prescription medications have not proven particularly helpful in PBS/IC. Certain nutraceuticals appear to be useful, but caution should be exercised for undisclosed formulations that may contain ingredients of uncertain source and purity or ingredients of unproven utility.

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