Review Article

Interstitial Cystitis-Critical Assessment of Current Treatment and Opportunities for Nanodelivery

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ABSTRACT

The characteristic feature of Interstitial cystitis (IC) or bladder pain syndrome is augmented, pressure, or inconvenience in the suprapubic or bladder region. The causative factors for IC are not completely understood however certain underlying disease condition may trigger the pain. The therapy is aimed to provide symptomatic relief, and therefore, the treatment protocols have been established based on experience. Intravesical delivery of drugs has been well explored and found to be most effective in minimizing the symptoms of IC without systemic adverse events. However, the efficacy of drug absorption is limited by the bladder wall permeability and poor absorption of the instilled drugs. The intravesical approach should be coupled with novel nanocarriers such as nanoparticles or liposomes to overcome these limitations. Nanoparticles can easily cross the bladder permeability barrier and enhance the drug retention time in the bladder, making the delivery efficient and promising. This review addresses the current IC management strategies, new potential therapeutic agents of natural origin, and various drugs undergoing clinical trials by different routes of administration.

Keywords: IC, Bladder pain syndrome, Bladder permeability barrier, Intravesical delivery, Nanotherapeutics.

INTRODUCTION

Pathophysiological Features of Interstitial Cystitis

Interstitial cystitis (IC) is a multifaceted inflammatory bladder syndrome with undetermined etiology. Bladder pain linked with urgency for urination, bloody urine, increased urination frequency, and nocturia are the characteristic manifestations of the IC. IC is still an enigma and represents a diagnostic and therapeutic challenge as its pathogenesis remains unclear.[1-2] IC is most commonly seen in women and affect their Quality-of-life (QoL) for a prolonged duration.[3-4] Both IC and chronic urinary tract infection exhibit similar signs and symptoms; however, there is generally no infection. Symptoms of IC worsen if there is a urinary tract infection. While there is no cure for IC, medications and other therapies can relieve the symptoms associated with it to improve the QoL of patients. Various triggers that have been identified for IC are allergies,[5] autoimmune disease,[6-7] defective bladder lining, mast cell aberrations and vascular disease[7-8] or unidentified infections. (Figure 1) Based on the cumulative information from various sources, the most common manifestation of IC as the bladder pain syndrome/disorder (BPS)[9] IC/BPS is considered as a part of hypersensitivity disorders that not only affect the bladder, but also other organs in viscera and has

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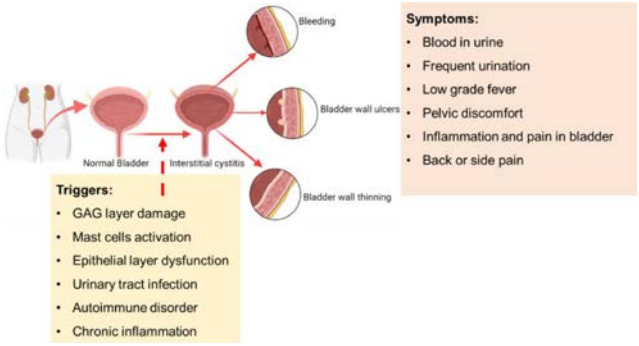

Figure 1: Pathophysiological features showing various trigger factors and the symptoms of IC/BPS.

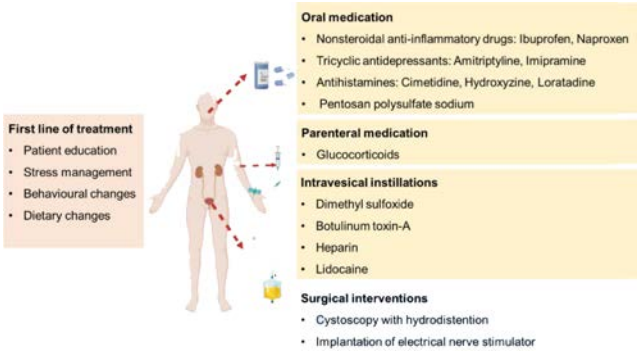

Figure 2: Various nonpharmacologic and pharmacologic approaches used in the management of IC along with different routes of drug administration.

overlapping pathophysiology.[10-11] While the alternative hypothesis for IC/BPS suggests that it may be a part of part of overactive bladder disorder, either painful or painless.[9]

Diagnosis and Current Treatment Modalities for the Management of IC

Although the exact cause of IC is inadequately perceived, however different hypothesis suggest various causative factors that may include disturbance in the urothelium lining permeability of the bladder due to deficiency of glycosaminoglycan (GAG), immune system actuation, pole cell penetration, neurogenic mechanisms or any infection.[12] Approximately 5–10% of patients will have ulcerations in the bladder, known as Hunner's injuries (HL)[13] related to more extreme indications and diminished bladder limit. Although it is beyond the realm of possibilities to recognize patients with HL on the basis of manifestations alone, utility of cystoscopy shift between rules, sometimes mandatory and sometimes optional.[14] To preclude the other underlying diseases like carcinoma, urothelial carcinoma, other malignancy, nephrogenic adenoma, or eosinophilic cystitis, carrying out biopsy of these lesions is a requisite. Treatment of IC is usually focused on expanding the QoL, as no treatment will cure the root cause of this condition. Regardless of nonulcerative or ulcerative status, IC stays inadequately perceived that needs powerful and proof-based medicines. A variety of different therapies exists ranging from counselling to surgical interventions (Figure 2). However, the proof supporting these therapies is frequently conflicting and therefore, new medicines covering different therapeutic mechanisms are consistently being researched.

IC being usually underdiagnosed, the reports on the best accessible treatment are lacking to draw any conclusions. Various non-pharmacological and pharmacological treatment (Oral, intravesical, and parenteral medications) options that are currently in practice are for the management of IC are shown in Figure 2.

Oral or intravesical treatments are the mainstay, while surgical management may be required for refractory cases. Investigations of mix or multimodal treatments are inadequate. Attributable to the scarcity of randomized controlled preliminaries on various medicines, a proof-based administration convention has not yet been created.

Non-pharmacological Therapies

Treatment approach for IC generally begins with more conservative therapies. The initial treatment strategy usually relies upon patient inclinations, manifestation seriousness, and decision-making ability of the clinician. Several accessible traditional treatments for the management of IC includes dietary control, stress decrease, and physical treatment. Lifestyle management such as bladder preparation with controlled liquid admission and Kegel practices have been found to be effectively ease the symptoms in almost one half of the patients.[15-16] Chronic IC patients exhibit a reduced bladder capacity and consistent low volume urination. Maintaining a voiding record and gradually increasing the span between voiding is a part of the bladder training that eventually helps in improving the bladder capacity. Additionally, following a strict diet has been suggested as a 'first-line taking care of oneself' in IC patients. Dietary control like staying away from acidic drinks, caffeine, liquor, chocolate, tea, pop, fiery food, and artificial sugar also.[17-18] When affronting food sources are suspected, the utilization of an end diet may distinguish which food sources or liquids add to erupting side effects, and the patient should then be guided to keep away from said food sources.[19] Nonetheless, not all patients need to attempt a confined eating routine, and only one out of every odd patient is touchy to similar food varieties. Since numerous IC patients alter their eating regimens

and are persistently sick, nutritional supplementation can be advantageous.[19]

Stress is possibly the main variable that disturbs the recovery of IC. Patients ought to be urged to carry out stress reducing procedures. Although, these methods may not be exclusively valuable precaution, yet it may be additionally helpful to patients with extreme manifestations. Changing lifestyles, shortening working hours, picking a less requesting responsibility, exercising, or joining support groups may help improve the QoL.[20-22] Several clinical trials have proved the benefits of physical therapy like exercises of pelvic floor muscles. Mental relaxation procedures, such as learning meditation[23-25] and complementary therapies acupuncture and delicate tissue massage may help to some extent.

Pharmalogical Therapies

Oral Medicines

Oral pharmacologic treatment remains the primary pillar for the management of IC. Oral therapy include drugs like, pentosan polysulfate sodium, antimuscarinics, hydroxyzine, cyclosporine A, amitriptyline, analgesics and antibacterial. Data on multimodal treatments are not available to date to decide upon the effectiveness.[26]

The main stay for the management of IC has been the oral administration of Pentosan polysulfate sodium. Pentosan polysulfate sodium has been approved by U.S. Food and Drug Administration for the management of IC. Although, the etiology of IC remains unclear, but pathologic abnormal epithelial GAG layer that forms the anti-adherent permeability barrier[27] is suspected to be the prime causative factor for IC. Pentosan polysulfate sodium is presumed to fix the GAG layer aberration and also minimizes permeation of bacteria or toxins into urothelium. Pentosan polysulfate was the first orally administered drug that was evaluated in a placebo-controlled clinical trials for the management of IC.[28-31] Few more studies have shown moderate symptomatic improvement.[32-34] Although it is well tolerated drug, long-term therapy is required to see the clinical benefits.

Tricyclic antidepressants interact with a variety of neurotransmitters receptors. Among them, amitriptyline is the widely explored drug for the management of IC that prevent the serotonin and noradrenaline reuptake by acetylcholine and H-1 receptors. Anticholinergic effects are presumed to affect the urgency and recurrence indications in IC. Also, the intercepted communication with neurotransmitters reuptake might have a pain-relieving effect.[35]

Antibiotics are not preferred therapeutic modality for the management of IC. Non-significant therapeutic effect of antibiotics has been reported in a randomized placebo-controlled study. On the contrary, adverse effects occurred more frequently through antibiotic use.[36] However, use of long-term antibiotics has been demonstrating serious side-effects, thus their further use has been discouraged.

Hydroxyzine, an H1 antagonist induces the release of neuroactive and vasoactive chemicals that prevents degranulation of the mast cells. However, hydroxyzine failed to show any statistically significant benefits over placebo in one randomized controlled trial.[37] Therapeutic evidence show inconsistent efficacy of cimetidine (H2 antagonist) and hydroxyzine in IC, therefore their therapeutic usage has not been recommended by some guidelines. Overactive bladders have been treated with antimuscarinics. Although, over active bladder and IC both exhibit symptomatic similarity, still antimuscarinics may not be effective in the management of IC. This is possibly due to the completely different pathophysiology of IC and overactive bladder, even if the symptoms overlap.[38]

Intravesical Medications

One of the treatment modalities for IC is the Intravesical treatment approach wherein drug is directly instilled into the bladder with the help of a catheter.[51] These medicines need to preclude other pathologies and are normally suggested when oral medication had not shown efficacy.[9,52-53] Most of the accessible medicines in this class help repair the abnormal GAG layer of the bladder urothelium of the IC patient. Anomalous GAG layer that lines the apical cells is presumed to be the causative factor for the induction of IC.[54-55] The components of GAG layer include, sulfated polysaccharides, which may be sulfates of chondroitin, keratin, dermatan, heparan, or hyaluronic acid. The intravesical instillation of the components of GAG layer exogenously, as monotherapy or blend, is presumed to restore the anomalous GAG layer.[35] FDA has approved the intravesicular administration of Dimethyl sulfoxide (DMSO) for the management of IC. Intravesicular administration of DMSO is normally carried out weekly for 6 weeks, alone or mixed in other medications.[56] DMSO has been reported to have anti-inflammatory effects, smooth muscle relaxant, collagen disintegrator, and nerve blocker. According to available reports, the efficacy of DMSO in IC remains unclear, and therefore its therapeutic usage has not been recommended by the guidelines.[9]

Heparin, an anionic polyelectrolyte, is a derivative of GAG ingredients and hence it is expected to restore the GAG layer. A study be Parsons *et al.*[57] reported

Table 1: Shows the current and upcoming medications used through oral or intravesical route in the treatment of IC.	
Medicines	**Reference**
Recommended medications for oral use	
Amitriptyline	39
Cimetidine	40
Hydroxyzine	37
Pentosan polysulfate sodium	28,31-32,41
Discouraged for oral administration	
Long-term antibiotics	36
Glucocorticoids	----
Intravesically instilled recommended therapeutics	
DMSO	42-43
Heparin	44
Lidocaine	44-46
Intradetrusor recommended medication	
Botox	47
Discouraged for intravesical instillation	
BCG	48
Emerging intravesical instillation systems	
LiRIS (Lidocaine releasing intravesical system)	45
Sphingomyelin liposome	49
Liposome/Botox	50

symptomatic improvement in the more than half of IC patients by heparin. The reports on intravesical heparin for the treatment of IC are limited; thus, additional control trials are required.

Glycoprotein, Hyaluronic acid, has been conventionally used for restoration of GAG layer. Several studies have proven the efficacy and toxicological of hyaluronic acid in the treatment for IC.[58-60] Another study reports the reduction in the bladder pain and voiding frequency with intravesical administration of lidocaine, but symptoms were found to be reoccurring within 3 months after treatment.[61-62] Short-term relief from IC have also been observed for the patients treated with lidocaine, pentosan polysulfate sodium and oxybutynin instillation.[62-64]

Surgical interventions

The surgery is the last option in the treatment of IC when the symptoms are not manageable with oral medications and patient's QoL is getting badly affected. The surgery involves cystectomy with cystoplasty. It may also be urinary diversion with or without cystectomy.[9,65] The surgical procedure are aimed at improving pain, urinary symptoms, and QoL.[66] very few patients show benefits to this treatment, many continue to report the pain Table 1.[67]

Limitation of the Existing Treatment Modalities of IC

Looking at the current developments in diagnostic devices and formulation science, one should be able to formulate and optimize novel therapeutics so as to have reduced side effects. Parenteral delivery suffers from the drawback that very little amount of drug is available at the bladder to show effect. Also, non-target body organs get exposed to the drug. Ultimately, the patient may need surgery if oral or intravesical treatments are ineffective.

The simplest approach is the direct delivery of the drug to the location of the pathology. Therefore, a local application would be more effective to ensure maximum contact of drug with the bladder wall. When the drug is administered through urethra into the bladder, systemic side effects are avoided. Less dose is required as all the drug is at the site of action and there is no possibility of first-pass metabolism. The bladder is a hollow organ and is quite easy to access through catheterization. It is hollow and can hold large volume of drug solution. In the case of intravesical treatment, the drug is instilled by solution into the bladder through a catheter. However, the instilled solution gets diluted with the urine thus reducing the concentration gradient for passive diffusion. Also, patient will urge to urinate when bladder holds a large volume of liquid. Frequent urination will empty the bladder and effect of drug will be lost, needing additional dose administration. Repeated catherization also puts patient at a risk of developing an infection. treatments with repeated catheterizations which increases the chances of infections. Drugs administered into the bladder need to cross tough barrier of urothelium to show any effect.[54,68-71] The penetration of drug into the bladder wall is further retarded by GAG layer on the surface of umbrella cells. Other parameters reducing the transport across urothelium are the pH of the instilled solution, solubility, molecular weight, and the partition coefficient of the drug.[72] One can improve the therapeutic efficacy and can overcome the above mentioned disadvantages by using novel therapeutic approaches like nanoparticulate systems or deformable liposomes.

Nanoparticles for the Treatment of IC

To prolong the duration of stay in the bladder and increase the penetration of drug across the bladder wall, one case makes use of novel transporters like liposomes, solid lipid nanoparticles, and other nanocarriers (Figure 4). Numerous nanoparticulate systems for direct bladder instillation have been reported (Table 2).

For last twenty-five years, application of liposomes has been extensively explored for intravesical route.

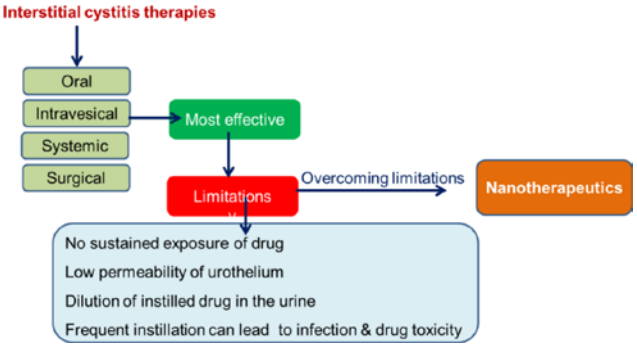

Figure 3: Overcoming the barrier of drug delivery in the current management of IC.

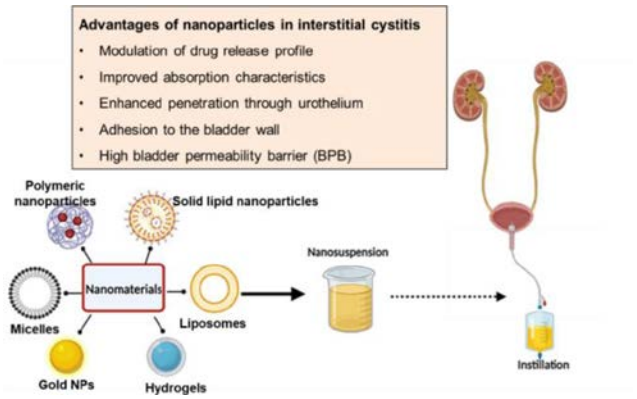

Figure 4: Various nanocarriers explored for the treatment of IC.

Liposomes are the fluidic lipid vesicles made out of synthetic or natural phospholipid that self-assemble to form bilayered structures, enclosing an aqueous core. Being biomimetic and deformable particles, liposomes assist in adherence of the liposomes to the cells that facilitates cellular uptake.

Liposomes can encapsulate both hydrophilic and hydrophobic drugs making the system suitable for most of the drugs.[74] Liposomes without any drug, made from phospholipid, sphingomyelin, could reduce mucosal inflammation and improved healing in patients suffering from IC.[81] Clinical studies using multilamellar sphingomyelin liposomes for intravesical therapy for IC have shown beneficial effects. In addition, liposomes have also been used as a delivery system for botulinum toxin and tacrolimus.

Several other nanoparticulate systems can be developed using biocompatible lipids, polymers and biopolymers, and proteins. Metallic particles like silver and gold nanoparticles and other organometallic systems can also be developed. Bioadhesive polymers, used while making nanoparticulate dosage form, can enhance the stay of the formulation in the bladder. These systems will have weak bonding with mucus on urothelium and will not have effect of bladder emptying on their residence. This will reduce the repeated drug administration.

Table 2: Various nanoparticulate systems explored for the treatment of IC.

Nanoparticle	Findings of the study	Reference
Nanocrystalline silver	Intravesical instillation of nanocrystalline silver provided an alternative or additive treatment for IC.	73
Liposomes	Botulinum Toxin Type A (BoNT-A) liposomal instillation was a simpler and effective treatment.	50
Liposomes	Intravesical liposomes of sphingomyelins without drug showed efficacy in clinical trials of IC.	74
Liposomes	Liposomal tacrolimus showed promising approach for treatment of inflammatory bladder conditions.	75
Mucoadhesive nanoparticles	Chitosan nanoparticles of model drug trimethoprim showed potential for extended delivery in bladder.	76
Micelles	Polycaprolactone micelle-encapsulated Quercetin efficiently reduced the signs of inflammation and edema in IC model.	77
Polymeric nanospheres	Biodegradable polymeric nanoparticles of trimethoprim showed improved cell adherence.	78
Polymeric nanoparticles	Conditioned medium stem cell -loaded nanoparticles showed improved efficacy in IC.	79
Hydrogel	Effectively prolonged residence time of heparin in acute bladder injury model.	80

Nanocrystalline silver (1%) formulation after administration to bladder cavity reduced urine histamine levels. It also decreased tumor necrosis factor and suppressed mast cell activation. This action may be useful for the treatment of IC.[73] Liposomes of botulinum toxin and tacrolimus showed that the drug stays protected in the liposomal core and thus degradation is reduced. This helps to improve the efficacy at low concentrations. Therefore, intravesical liposomal drug delivery might be an exciting treatment strategy for prolonging the local bladder delivery to treat most of the inflammatory bladder disorders.[50,75] Cationic chitosan nanoparticles showed better bioadhesion compared to pristine chitosan nanoparticles when used for bladder retention. Also the cationic liposomes were more successful in

extending the release of drug, thus providing a platform technology to incorporate drug and use for bladder delivery Figure 3.[76]

PLGA and cationic chitosan nanoparticles were also explored as anti-inflammatory system for bladder inflammation. The dosage form successfully suppressed levels of pro-inflammatory cytokines in cystitis model. These nanoparticles were biodegradable and also improved urinary frrquency.[79]

Clinical trials involving various drugs and dosage forms given by different routes of administration for the treatment of IC

Regardless of the years of basic and clinical examination for the treatment, difficulty in understanding of the pathophysiology and nonavailability of an effective drug for curing IC still exists. Traditionally, there has been an absence of sufficient expertise and utilization of novel, incorporated techniques to study IC. However, some significant insights have been acquired over a period of time and with the advances made in nanotechnology. For instance, epidemiological investigations have uncovered that IC is usually associated other pain and inflammatory type of diseases like irritable bowel syndrome. These perceptions propose that IC might include fundamental pathophysiology and alterations of the central nervous system in some patients. There might be numerous causes that are responsible for enhancing the symptoms of IC. A novel, innovative research and thorough understanding is necessary to completely describe the relationship between IC syndrome and other overlapping symptoms disorders. A more comprehensive clinical trials are required to provide better insights into basic disease scenarios. Table 3 shows the details of ongoing and completed clinical trials in the treatment of IC in the treatment of IC due to reduced toxicity and enhanced efficiency.

Natural Remedies having Potential for the Management of IC

The treatment approach for IC is mainly focused on reducing the indications of recurrence, urgency, and pain. Complementary systems offer multipathway approaches for treatment of IC. Such systems are useful in for providing customized treatment for individual patients To date, few studies have examined the use of alternative medicines for IC.[82] One formula may not fit for all, however, may be used as additional treatment regimen to provide symptomatic relief and to arrest progression of IC. Instead, alternative systems of medicine work in better way when they are combined with current management strategies.

Table 3: Ongoing and completed clinical trials study for the treatment of IC.

Drug	Clinical Trial no.
Drug administration by oral route	
Peppermint Oil	NCT04845217
Cyclosporine	NCT01990898
MN-001 BID	NCT00295854
Metoprolol Tartrate Oral Tablet	NCT03008382
PD 0299685	NCT00739739
Amitriptyline	NCT00124306
Aloe Vera Capsules	NCT04734106
ASP3652	NCT01613586
Naltrexone	NCT04450316
Oxycodone naloxone prolonged release tablets	NCT01197261
Naltrexone	NCT04313972
AQX-1125	NCT01882543
D-Cycloserine	NCT02385266
sodium chrondroitin sulfate (Uracyst®)	NCT00150488
Drug administration by intravesical route	
LP-08	NCT01393223
Liposomal capsaicin	NCT01731470
Botulinum toxin A	NCT01969773
Liposome encapsulated BoNT-A	NCT02247557
Resiniferatoxin	NCT00056251
TTI-1612	NCT01559961
Hyaluronic Acid and Chondroitin Sulfate	NCT03463499
2% sodium chondroitin sulfate	NCT00919113
Liposomes	NCT01731470, NCT01083979
Ozone	NCT04789135
Heparin and Alkalinized Lidocaine	NCT04401176
URG101	NCT00517868
SI-722	NCT04208087
Capsaicin	NCT00004316
Triamcinolone acetonide	NCT03463915
TC-3 Gel mixed with Botox	NCT01997983
Alkalinized Lidocaine-Heparin	NCT00256542
Cystoscopic drug administration	
LiRIS	NCT01150565, NCT01879683
Systemic administration of drug (Subcutaneous, intravenous or intranasal)	
Adalimumab	NCT01295814
Oxytocin	NCT00919802
Ketorolac Tromethamine	NCT02000401
Dexmedetomidine	NCT01195116
Onabotulinumtoxin A	NCT02297100, NCT02600715
PF-04383119	NCT00601484
ASP6294	NCT03282318
Certolizumab pegol	NCT02497976
Dextrose	NCT04821882
Omalizumab	NCT01294878
BOTOX	NCT05141006
Tanezumab	NCT01030640

Melatonin, a supplement antioxidant substance was found to protect the bladder lining from irritants in a study on rats.[83] This study suggests that melatonin holds promise as an alternative treatment for IC. The bioflavonoid quercetin found in seeds, citrus fruits, tea, and red wine. It has shown to inhibit histamine release from mast cells.[84] It has anti-inflammatory,[85] anti-oxidant, anti-viral[86] and anti-tumor properties.[87] It reduces inflammation by neutralizing free radicals within the body. This approach helps to stop the inflammation before it starts. A clinical trial of the quercetin-containing dosage form was carried out in 22 IC patients for 4 weeks. More than 50% of the patients showed improvement in QoL as their pain was reduced.[84] In a recent study, quercetin loaded biodegradable miceller formulation was used to manage IC.[77] Quercetin micellar treatment in acute cystitis model showed a reduced inflammation when analyzed as edema. Capsaicin, an active ingredient of red pepper, was reported to reduce suburothelial nerve densities in the bladder of patients with detrusor hyperreflexia by releasing calcitonin gene-related peptide stored in afferent fibers at a cellular level.[88] This could be beneficial in prolonged effect in IC patients.[89] Capsaicin liposome showed promising effects in rats when delivered as temperature sensitive gel.[90]

L-Arginine is a common amino acid. It is present in in many foods and is a precursor to nitric oxide. This molecule helps to dilate blood vessels. This increases blood circulation which help to reduce pelvic inflammation in IC. In a scientific study (n=50), 48% reported a improvement in their pain and IC related symptoms (pain intensity, pain frequency, and urinary symptoms).[91] IC and pelvic pain cause inflammation to build and linger around the bladder and pelvic floor, causing additional pain and dysfunction. Taking Omega-3 supplements can help balance out the bad oils in our daily diet and fight inflammation.[92] Aloe vera, a cactus plant, is one of the world's oldest known herbal remedies. Preliminary research of aloe vera in animal models has found that oral aloe vera increased the production of GAG molecules and thus helped to heal wounds.[93] GAG molecules are a major component of the bladder lining and therefore aloe vera consumption may play a major role in bladder health. In a large survey (n=600 IC patients) Aloe vera reported significant relief in pain, urethral burning, and urinary urgency/frequency (82%).[14] Lyophilized aloe vera was tested in a single small, double-blind, placebo-controlled study. 7 of 8 patients reported some symptomatic relief. 4 of 7 reported significant relief of most or all of their symptoms.[94] However, a controlled study needs to be conducted for a conclusive result. CystoProtek, a supplement formulation is commonly used by patients with IC. It combines several natural constituents that are anti-inflammatory and bladder protective. Chondroitin sulfate, sodium hyaluronate, and glucosamine sulfate, that are all GAG molecules. Additionally, flavonoids quercetin and rutin provide antioxidant and anti-inflammatory effects.[94] However, little scientific evidence has been provided on how these supplements affects IC, but many patients report relief anecdotally.

CONCLUSION

Treatment for IC remain elusive even after years of scientific research. However, nanotechnology seems to be a potential approach to resolve the challenge of treating IC. Nanotechnology, a new technique that involves creating and manipulating materials at nanoscale levels to create products that exhibit novel properties has shown beneficial results. Intravesical deliveries coupled with nanotherapeutics are offering tremendous potential in the treatment of IC. The synergistic approach of intravesical delivery with nanomaterials has proven effective, remedial and safe. The adhesion, penetration and retention are requisite for successful delivery in the bladder. Having said properties, nanomaterials can easily transport through the urothelium, adhere to the bladder surface, and provide sustained release of the drugs. Residence time of drug in bladder can be successfully increased using the approach of nanoparticles loaded with mucoadhesive excipients. Efforts to screen nanoparticle efficiency are underway to study drug contact time in the bladder, monitor enhanced urothelium permeation, and decrease systemic untoward effects. Detailed *in-vitro* and *in-vivo* studies must be performed and should further screen for clinical trials with combination therapies and novel techniques constantly emerging. Timely translation of studies to clinical research promises to change the face of healthcare in IC and bring the rewards of nanotechnology to the true beneficiary of all medical achievement and the patient. Additionally, natural products provide new personalized avenue as a complementary therapy for the management of pain in IC. However, controlled clinical trials are warranted to prove the safety and efficacy of long-term treatment of alternative system of medicine in chronic disorders.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GAG: Glycosaminoglycan; **BPS:** Bladder pain syndrome/disorder; **QoL:** Quality-of-life; **HL:** Hunner's injuries; **DMSO:** Dimethyl sulfoxide.

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