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Review Article

Role of enzyme-flavonoid therapy in controlling inflammatory pathology of pelvic inflammatory disease

Shalini Pankaj Srivastava[1,*], Shaily Pourush Agarwal[2]

[1]*Dept. of Obstetrics and Gynaecology, Om IVF - Om Surgical Center & Maternity Home, Varanasi, Uttar Pradesh, India*
[2]*Dept. of Obstetrics and Gynaecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India*

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ABSTRACT

Pelvic inflammatory disease (PID) is a clinical syndrome ensuing infection-induced inflammation of the upper reproductive tract in females. It is mostly characterized by chronic pelvic pain and can lead to severe outcomes like tubal-factor infertility or ectopic pregnancy. The treatment primarily focuses on eradication of infection and control of the inflammatory consequences. Nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly used for the control of inflammation, but their use is limited by adverse effects, especially when used in the long-term.

Systemic Enzyme Therapy (SET) using a combination of Trypsin-Bromelain-Rutoside have a long history of clinical use in various inflammatory conditions, including PID. It is an effective alternative to conventional therapies for managing the symptoms and preventing the complications of PID. SET moderates the inflammatory response, prevent scar formation and adhesions. The various mechanisms by which SET acts on the relevant pathophysiology of PID have been presented in this review. Results from clinical studies have also been discussed, including comparative studies of SET against placebo or conventional anti-inflammatory agents, and when given concomitantly with antibiotics versus antibiotics alone in a variety of acute and chronic PID-related conditions.

1. Introduction

Pelvic inflammatory disease (PID) is a clinical syndrome of the female upper reproductive tract which includes the endometrium, fallopian tubes, ovaries, and pelvic peritoneum and characterized by inflammation of the tissues.[1,2] Isolated inflammations of these tissues is rare due to their anatomical proximity and functional unity. Typically, PID is observed in sexually active females when microorganisms ascend from the vagina or cervix to the fallopian tubes and other upper genital tract structures.[3] Approximately, 85% of the cases involve sexually transmitted cervical pathogens or bacterial vaginosis–associated microbes, while 15% of infections are due to respiratory or enteric organisms. Some prospective study data shows that, if remain untreated, about 15% of Chlamydial infections may progress to PID.[4–6]

Some risk factors identified for PID are intercourse with multiple partners, use of contraception, age, vaginal douching, previous history of PID, intrauterine device (IUD) implantation, and tubal ligation.[7,8] Being the most common serious infection of women, mostly characterized by chronic pelvic pain, PID is a cause of about 30% of female infertility and 50% of ectopic pregnancies.[9] Globally, PID occurs in 1% of the adults in the 15-25-year age group. In India about 24-32% of women are estimated to be affected by PID.[10] The National Health and Nutrition Examination Survey (NHANES) 2013–2014 estimated a

* *Corresponding author*.
E-mail address: drshalini.ps@gmail.com (S. P. Srivastava).

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prevalence of self-reported lifetime PID of 4.4% among sexually experienced women in the 18 to 44-year age group. This comes to around 2.5 million women, in this age group, ever having PID in their lifetime.[1]

The symptoms of PID include pelvic or lower abdominal pain of varying severity, purulent vaginal discharge, dyspareunia, and dysuria. Uterine tenderness, Cervical motion tenderness or adnexal tenderness includes Cardinal signs.[4,7,8] In its chronic form, the condition is characterized by persistent pain and signs of dysfunction of the vascular (mainly microcirculation), nervous, immune, and endocrine systems. It presents as a protracted, often relapsing course, resistance of the infection process to traditional antibacterial therapy, the presence of immunosuppression and frequent complications (infertility, adhesions, tubo-ovarian formations). A subclinical PID having a clinically silent spread of infection to the upper genital tract in the absence of signs and symptoms is also observed in many women.[2,3] Due to this, any young female with lower abdominal pain and pelvic discomfort is suspected for PID.[7] Almost 60% PID patients are asymptomatic.[8]

Certain proteolytic enzymes and their combination with flavonoids, when administered systemically, have been found to be useful in a variety of painful and inflammatory conditions both acute and chronic. A commonly used combination of trypsin (an animal-derived serine protease), bromelain (a plant-derived cysteine protease) and rutin/rutoside (a flavonoid) has been evaluated as systemic enzyme therapy (SET) in conditions like chronic inflammation of the joints, post-surgical wound inflammation, chronic sinusitis, thrombophlebitis, and various sports injuries, with favorable results.[11] Different oral formulations of this combination, including dispersible tablets (Disperzyme®) and enteric-coated tablets (Phlogam®), are available in India. SET has been used empirically since many decades in various inflammatory conditions; but it is only now, with advancement of technology and research methodologies that we are uncovering the various mechanism by which these agents exert their action. SET with trypsin-bromelain-rutoside combination has also been tested in PID and associated conditions, with impressive results. These studies and the known mechanisms of individual agents, in relation to the pathophysiology of PID, have been discussed further in this review.

2. Pathophysiology of PID

PID is an infection-induced inflammation of the female upper reproductive tract and has a multi-microbial etiology. Considering Chlamydia as the prototype, it has been found that the host response is initiated and sustained by epithelial cells by the initiation and propagation of immune responses. They secrete chemokines that recruit inflammatory leukocytes to the site of infection and cytokines that induce and augment the cellular inflammatory response, and these mediators induce direct damage to the tissues. If there is a reinfection, a more amplified response is seen.[12,13] Activated toll like receptors (TLRs), especially TLR4 and TLR2 which are found in the upper genital tract, could be activated by common PID pathogens. Inflammatory cells infiltration in the upper genital tract is a diagnostic criterion for PID as well as necessary for the removal of pathogens. Neutrophils, which generate oxygen free radicals and proteolytic enzymes to remove pathogens, and lymphocytes are important in containing the infection. However, excess infiltration with these is associated with tissue damages and undesired sequelae.[14]

Excessive release of inflammatory cytokines, such as IL-1β and IL-6, from activated inflammatory cells and the cells in infected tissues, can enhance the production of chemokines, and activate the other cells to expand the inflammatory response. Oxidative stress and proinflammatory cytokines are well known to be potent activators of the nuclear factor (NF)-kB, a transcription factor. This activation promotes the productions of inflammatory cytokines and chemokines, thus providing a positive feedback to the pathway, self-perpetuating the inflammatory response.[15] The ratio balance between Th1 and Th2 cytokines determines the outcome of illness. It has been found that there is significantly increased expression of Th1 cytokine IFN-γ in PID patients, along with increased expression of Th2 cytokines interleukin (IL)-5 and IL-10.[16]

Chronic infections would lead to ongoing release of mediators that promote continued influx of inflammatory cells, damage to host epithelium, scarring, and, ultimately, fibrosis and scarring.[12,13] This may lead to the loss of the ciliated epithelial cells along the fallopian tube lining, leading to restriction in ovum transport which further tends to cause tubal-factor infertility or ectopic pregnancy. Due to healing action of inflamed tissue, there is formation of scar. These scar tissue bands bind the fallopian tube, ovaries, and uterus together to form adhesions. Adhesions caused due to infections leads to chronic pelvic pain.[4,7,10]

3. Medical Management

The medical management of PID primarily focuses on eradication of infection and control of the inflammatory consequences, which have the potential to cause reproductive disorders. The role of surgery is limited to drainage of pelvic collections and the early division of adhesions. Due to the polymicrobial nature of PID, it is treated with antibiotics covering broad spectrum of pathogens. Cephalosporins, fluoroquinolones and doxycycline are frequently used in these patients. Metronidazole is used optionally with all these antibiotics for full coverage against anaerobes and bacterial vaginosis.[5] However, the efficiency of these antibiotic drugs decreases every year, with the development of microbial resistance.

It has become a necessity to develop alternative treatment schemes and methods to improve the efficiency of existing drugs. Inflammation, although central to the development of complications associated with PID, has no specific recommended treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the inflammation and subsequent fibrosis associated with PID and its complications. Prevention of adhesions by NSAIDs has been demonstrated in animals but there is limited data of their effectiveness in human subjects. Also, regular use of NSAIDs may show some major adverse effects such as gastrointestinal hemorrhage, renal impairment. Hence, adjunctive therapies such as NSAIDs often do not improve clinical outcome.[4,8,12]

4. Systemic Enzyme Therapy (SET)

SET intervenes in different processes: the release of inflammatory mediators, the modulation of adhesion molecules, and the activation of fibrinolysis with consequent improved healing. SET moderates the inflammatory response by breaking down proteins that causes inflammation. It breaks down and removes fibrin and prevent scar formation and adhesions. Enzymes support and accelerate the natural inflammatory process without letting it get out of control. They affect the entire inflammatory process while maintaining the endogenous defense and repair mechanisms.[17,18] The various mechanisms, relevant to the pathophysiology of PID, have been presented further, in brief.

4.1. Trypsin – animal-derived serine protease

Trypsin, as a regulatory protease, activates other proteins through proteolysis at specific Lys or Arg bonds. Orally administered trypsin, exists in blood in bound form to specific (e.g, α2-antitrypsin) or unspecific (e.g, α2-macroglobulin) antiproteinases.[19] It enhances fibrinolysis (also an action of bromelain), affects coagulation factors, and has immunomodulating actions, especially on T-cell activation.[20–23] The breakdown of fibrinogen plays a substantial role in improving the macro and micro circulation and ensures the removal of inflammatory products as well as an adequate supply of oxygen and nutrients.[17] Together with bromelain, trypsin lowers the levels of proinflammatory cytokines (such as TNF-α, IL-1, IFN-γ).[24] The activation threshold of T-cells is increased in the presence of trypsin.[22] It can cleave and activate a growing family of G-protein-coupled protease-activated receptors (PARs), which play a major role in healing.[25]

4.2. Bromelain – plant-derived cysteine protease

Various fibrinolytic, antiedematous, antithrombotic, and anti-inflammatory activities of bromelain were demonstrated by in vitro and in vivo studies. The fibrinolytic activity is mediated by stimulating the conversion of plasminogen to plasmin.[26,27] Additionally it inhibits thrombus formation, by inhibiting platelet aggregation.[28] It exerts potent antiinflammtory effect by inhibiting leukocyte migration, possibly by altering cell surface molecules.[29,30] Bromelain also shows anti-inflammatory action by having an influence on prostaglandin and thromboxane synthesis, especially PGE2, PGF2 and thromboxane B2.[26,31] The potent inhibitory action of bromelain on Phospholipase A2, a key enzyme in the induction of arachidonic acid pathway leading to the formation of inflammation mediators, may be responsible for this.[32] In a placebo-controlled crossover randomized clinical trial, bromelain led to a significant shift in the circadian profiles of the Th1 cell mediator IFN-γ and trends in those of the Th2-type cytokine IL-5 and immunosuppressive cytokine interleukin (IL)-10, thus suggesting a general effect on the antigen-specific (T cell) compartment of the human immune system.[33] Bromelain has been shown to proteolytically block the activation of extracellular regulated kinase-2 (ERK-2) in T Cells, thereby inhibiting cytokine production and T cell signaling. The expression of IL-4 produced by Th2 cells and IL-2 and IFN-γ produced by Th1 cells, was reduced by 94%, 68% and 56%, respectively.[34] It has also been shown to enhance absorption and tissue penetration of antibiotics, without hampering the safety profile.[35]

4.3. Rutoside - bioflavonoid

Rutoside is primarily known for its potent antioxidant and organ-protective effect.[36] The antioxidant action has been demonstrated by reductions in production of superoxide ion, hydroxyl radicals and lipid peroxy radicals, as well as iNOS-mediated nitric oxide (NO), in multiple settings.[37–40] It has been found to inhibit the transcription of many inflammatory genes encoding critical proinflammatory factors, including TNF-α, IL-1, IL-8, and chemotactic factors.[38] The resultant reduction in inflammatory cytokines has been demonstrated in various studies.[38,40–43] The inhibitory action of Rutoside on NF-kB and TLR4 has also been demonstrated.[40,42] Rutoside has peripheral and central antinociceptive activities, and thus, helps in management of pain.[36] It also complements the anti-platelet effect of bromelain.[43,44]

5. Clinical Studies of SET in Various Pelvic Inflammatory Conditions

SET with Trypsin-Bromelain-Rutoside combination has been studied in a variety of acute and chronic clinical conditions of PID like adnexitis and endometritis and other related conditions like cystitis. These studies include comparative studies of SET against placebo or conventional anti-inflammatory agents, and when given concomitantly with antibiotics versus antibiotics alone.

SET with Trypsin-Bromelain-Rutoside combination was compared to Diclofenac in a randomized, double-blind clinical trial in patients with laparoscopically-confirmed chronic PID. Therapy was given for the duration of 3 weeks. The primary variable was a sum score computed from the symptoms gynecological palpation (pain under motion, pain under pressure, abdominal defense), erythrocyte sedimentation rate (ESR) score and white blood cell (WBC) score at end of therapy. Other studied variables included abdominal pain, micturition difficulties, painful defecation and C- reactive protein. After 3 weeks of therapy, there was no statistical difference between the groups in any of the variables. Both therapies were rated as 'good' as per physician and patient assessment of efficacy as well as for tolerance. There were three patients, all from the Diclofenac group, who reported adverse events - two had gastrointestinal complaints and one developed blepharedema. No adverse event was noted in the SET group.[11]

The efficacy and safety of Trypsin-Bromelain-Rutoside combination, supplemented with vitamins, were investigated in patients with stage I - II endometriosis and posted for surgery, in a double-blind placebo-controlled study. In this 30-subject study, treatment was initiated 40-60 days prior to surgery and continued for 60 days after surgery. Both clinical improvement in pain and levels of plasma and peritoneal fluid markers were checked. Lower VAS scores of pain were observed before surgery and perioperatively. Patients who received SET did not show the increases in plasma levels of sCD40L, EGF, IGFBP-1, IL-6, IL-8, TGF-α and TNF-α in the perioperative period, unlike those who received placebo. These analytes are markers of chronic activation of B cells, cellular proliferation, and inflammation. A similar trend was observed for several of the tested analytes in the peritoneal fluid, with lower concentrations in those received SET.[45]

The effect of hydrolytic enzymes and antibiotic therapy was evaluated in a study in patients with adnexitis. This randomized double-blind study was conducted in 56 patients, randomly divided to receive either the enzyme combination or placebo, in addition to antibiotic therapy. The treatment continued for 28 days. Effectiveness and tolerance in the initial 6-day treatment was evaluated. With similar findings at baseline, there were significant improvements in body temperature, leukocyte count, ESR, score of palpable tumours, tenderness and vaginal discharge in the enzyme group. Adnexitis score, the primary efficacy criterion, also showed significant improvement at the end of therapy. No side effects were noted in either group.[11,46,47]

SET given in combination to standard antibiotic therapy was also evaluated, not only for its immediate efficacy and safety, but also for its impact on inflammatory markers and relapse rates after 6 months, in 60 women with an exacerbation of chronic recurrent bacterial cystitis. The women were divided into two groups of 30 each, one which received only standard antibiotic therapy and the other which received SET, additionally. By day 14, both groups showed resolution of clinical and laboratory signs of cystitis. But patients in the SET group had a more rapid relief from inflammation, as indicated by the decrease in the frequency of urination, urgency, nocturia, severity of inflammatory changes in the blood and urine by day 7 of treatment. The 6-month relapse rate was much lower (13.3%) in the SET group compared to 30% in the control group.[48]

In a 30-patient study, SET in combination with antibiotics, anti-fungal and vitamin therapy was evaluated in the treatment of chronic salpingitis with infertility. In this study 30 women of mean age 26.5 years having chronic salpingitis and infertility were observed. Oral SET was administered for 10 days to patients in one group along with the other drugs, while the control group patients received the same drugs without SET. After 5-6 days of SET treatment, there was improvement in frequency and intensity of abdominal pain, normalization of body temperature, appetite and intestinal function, decreased infiltration, disappearance of tenderness, decreased leukocyte count, normalized erythrocyte sedimentation rate and decreased C-reactive protein. These parameters remained unchanged in control group. Normalization of microflora and menstrual cycle was also found in 20 out of 22 patients treated with SET.[11]

SET was also studied in combination with wide-spectrum antibacterial therapy, in the treatment of actinomycotic infection-induced pelvic inflammation. The study included 36 patients, out of which 14 received SET in addition to antibiotics, while the other 22 received only antibiotics. Histological evaluation of endometrium smears and biopsies were carried out to check progress. The average duration of treatment was 4.5 months for patients who received SET therapy, compared to 8.5 months in the control group. Repeated surgical operations were carried out in control group (31.8%) which was not the case in patients receiving SET therapy.[11]

6. Conclusion

Therapy with Trypsin-Bromelain-Rutoside combination has shown impressive results in the management of PID. There is an increasing body of evidence elaborating the various mechanism by which these agents act. With a relatively better safety profile of these agents, derived from natural sources and long history of clinical use, Trypsin-Bromelain-Rutoside combination provides a promising alternative to conventional therapies for managing the symptoms and preventing the complications of PID.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Author biography

Shalini Pankaj Srivastava, Consultant Obstetrician, Gynecologist & Infertility Specialist

Shaily Pourush Agarwal, Associate Professor

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