CHAPTER-2

REVIEW OF LITERATURE

2.1 Introduction

2.1.1 What is Ulcerative Colitis?

Ulcerative colitis is a long-term (chronic) condition affecting the colon. The symptoms of ulcerative colitis can range from mild to severe, with the condition being unpredictable. Symptoms can flare up and then disappear or known as remission for months or even years. Ulcerative colitis is the result of an abnormal response by your body’s immune system. Normally, the cells and proteins that make up the immune system protect you from infection. In people with IBD, however, the immune system mistakes food, bacteria, and other materials in the intestine for foreign of invading substances. When this happens, the body sends white blood cells into the lining of the intestines, where they produce chronic inflammation and ulcerations. It’s important to understand the difference between ulcerative colitis and Crohn’s disease. Crohn’s disease can affect any part of the GI Tract, but ulcerative colitis affects only the colon. Additionally, while Crohn’s disease can affect all layers of the bowel wall, ulcerative colitis only affects the lining of the colon. While both ulcerative colitis and Crohn’s disease are types of Inflammatory Bowel Disease (IBD), they should not be confused with Irritable Bowel Syndrome (IBS), a disorder that affects the muscle contractions of the colon. IBS is not characterized by intestinal inflammation.

2.2. Concepts of all the treatments for ulcerative colitis.

Initial treatment of ulcerative colitis is medical, using antibiotics and anti-inflammatory medications such as aminosalicylates. If these fail, prednisone can be used for a short period of time but long-term use can be associated with significant side effects. If prednisone is ineffective or cannot be discontinued,
immunomodulators such as 6-mercaptopurine or azathioprine can be used to control active disease that does not merit hospitalization. In order to maintain control of the disease, aminosalicylates or immunomodulators are used on a long-term basis. “Flare-ups” of the disease can often be treated by increasing the dosage of medications or adding new medications. Hospitalization may be necessary to put the bowel to rest and deliver steroids directly into the blood stream. Ulcerative colitis is treated as an autoimmune disease. Treatment is with anti-inflammatory drugs, immunosuppression, and biological therapy targeting specific components of the immune response. Colectomy is occasionally necessary if the disease is severe, doesn’t respond to treatment, or if significant complications develop. A total proctolectomy can be curative, but it may be associated with complications.

2.2.1 Medical Management:

Prior to initiating therapy, a patient must be evaluated for extent and severity of disease. Extent of disease is best assessed by colonoscopy with biopsy of grossly affected as well as unaffected areas. If disease is distal to the splenic flexure, topical therapy such as suppositories and enemas may be the first choice. For more extensive disease, oral agents or a combination of oral and topical agents are indicated. There are some of the allopathic medicines used for the treatment of ulcerative colitis.

2.2.1.1 Aminosalicylates

Sulfasalazine and 5-aminosalicylate (5-ASA) drugs are the first line in drug therapy for the treatment of mild to moderate UC. By Meta analysis, rectally administered 5-ASA is superior to placebo and rectal corticosteroids for induction and maintenance of remission in distal UC. If the patient has proctitis, 5-ASA suppositories at a dose of 500 mg twice daily will induce and maintain remission. For disease up to the splenic flexure, 5-ASA enemas are effective for induction and maintenance of remission in doses of 2 to 4 g per enema.
For more extensive disease, multiple oral 5-ASA preparations are available. Sulfasalazine was the first 5-ASA agent found to be effective in UC. Placebo-controlled trials have shown that sulfasalazine is effective in inducing and maintaining remission in mild to moderate UC. However, its use is limited by high rates of intolerance among patients. Side effects can include headache, abdominal pain, nausea, vomiting, skin rash, fever, hepatitis, hematologic abnormalities, folate deficiency, pancreatitis, systemic lupus erythematosus, and male infertility. Sulfasalazine should always be given with folate 1 mg daily and is contraindicated in men attempting conception.

Sulfasalazine is a combination of 5-ASA azo-bound to the antibiotic sulfapyridine. It is the 5-ASA component that is the therapeutically active compound and the sulfapyridine moiety that is the cause of many of the side effects. This finding led to the development of alternative 5-ASA delivery systems for the treatment of UC and the discovery that it is the overall dose of mesalamine given, rather than the delivery system, that determines efficacy. Oral mesalamine agents with delayed- (Asacol) or timed-release (Pentasa) formulations at doses of 1.6 to 4.8 g/day are effective in maintaining remission. Combination therapy, with oral mesalamine 2.4 g/day and rectal mesalamine 4 g/day, is more effective than either therapy alone. However, this may simply be a reflection of the overall dose of mesalamine received by the patient.

Olsalazine and balsalazide are 5-ASA agents that have diazo bonds, which are released by colonic bacteria. Olsalazine is effective for induction and maintenance of remission in UC, but its use is limited by worsened diarrhea. Balsalazide is composed of a 5-ASA linked to an inert carrier molecule. Although one study show significant efficacy of balsalazide over an equivalent dose of mesalamine, other studies have shown an efficacy equal to sulfasalazine and mesalamine for induction of remission in mild to moderate UC.

Though 5-ASA agents are considered safe, some toxicity can be seen. Aside from the complications attributed to sulfasalazine above, the most frequently reported side
effects of 5-ASA agents include dizziness, fever, headache, abdominal pain, nausea, and rash. Rare but serious adverse events include pulmonary toxicity, pericarditis, hepatitis, pancreatitis, aplastic anemia, leucopenia, and thrombocytopenia. Though interstitial nephritis has been reported, the frequency of renal insufficiency was low in large safety and pharmacovigilance databases of Asacol and Pentasa. Finally, a minority of patients will experience worsening diarrhea and abdominal pain due to a hypersensitivity reaction to 5-aminosalicylate.

In summary, 5-ASA agents are safe and effective for the induction and maintenance of remission in mild to moderate UC. Its use in severe colitis is not well studied. Data support the concept that the optimum use of aminosalicylates in active UC demands the highest tolerated dose, whether administered orally, rectally, or in combination. In quiescent disease, lower doses may be tolerable to the patient and are less costly, although again, there is the general theme of dose response.

2.2.1.2 Corticosteroids

The discovery that corticosteroids were effective in UC had a significant positive impact on a disease with a previous high mortality. Mortality rates dropped from a high of 61% to 4 to 7%. However, today the side effects of corticosteroids make it a less desirable though sometimes unavoidable agent in the therapy of UC.

In a population-based study in Olmstead County, Minnesota, 34% of UC patients required corticosteroids at some point in their disease course. Therapy with corticosteroids resulted in complete remission in 54%, partial remission in 30%, and no response in 16%. At 1 year from initiation of corticosteroid therapy, prolonged response without steroids or surgery was seen in 49%, corticosteroid dependence in 22% and surgery in 29%.

Resistance to corticosteroids is seen in 16 to 20% of patients. Several potential mechanisms for resistance to corticosteroid therapy in patients with inflammatory
bowel disease (IBD) have been described, including an increase in the expression of glucocorticoid receptor β and increased expression of the multidrug resistance-1 gene (MDR-1). The latter results in an increased expression of the membrane-based drug efflux pump P-glycoprotein 170 that pumps corticosteroids out of cells, thus lowering the intracellular concentration.

Corticosteroids can be administered as oral (cortisone, prednisone, prednisolone, budesonide), intravenous (prednisolone, methylprednisolone, corticotrophin), or rectal (beclomethasone, tixicortol, budesonide, prednisolone metasulfobenzoate) formulations. It has been reported the efficacy of cortisone 100 mg per day in UC in 1955. Other report shows that 40 mg of prednisone was more effective than 20 mg and equally effective as 60 mg, but with fewer side effects. Finally, single daily dosing of prednisone 40 mg daily was equally effective as 10 mg four times a day. It is from these early studies that the current maxim of prednisone 40 mg per day for moderate to severe UC originated. No maintenance benefit of corticosteroids in UC has been found.

Rectal corticosteroids are effective in left sided UC. They provide quick relief for patients with tenesmus and bleeding. Rectal hydrocortisone 100 mg and prednisolone 10 mg have been proven effective by controlled trials for induction of remission, but not for maintenance. Budesonide enemas, which have minimal systemic absorption, are also effective for induction but not for maintenance of remission in left sided UC. However, by Meta analysis, topical corticosteroids were not as effective as topical mesalamine therapies for ulcerative proctitis and left sided UC. Also, rectal corticosteroids are well absorbed and can result in suppression of the adrenal axis.

Prednisone and prednisolone are well absorbed after oral administration and bioavailability is high, averaging over 70%. However, the absorption may be decreased in patients with severe UC in whom oral administration of prednisolone resulted in a lower peak plasma concentration and a slower rate of decrease in the plasma concentration compared with healthy volunteers. Patients with severe UC
who receive 60 mg/day of intravenous prednisolone have a 73% response rate in 5
days. Some patients are slower responders and will require 7 to 10 days to respond.
No controlled trials have addressed the effectiveness of single, multiple, or
continuous infusion of corticosteroids in severe UC. Intramuscular corticotrophin
(adrenal corticotrophin hormone, ACTH) at 80 U/day showed a similar benefit to
cortisone 200 mg/day in patients with active UC. In severe UC, corticotrophin 80 to
120 U/day was similar to hydrocortisone 300 to 400 mg/day. However, some deaths
were reported in IV ACTH due to adrenocortical necrosis.

Corticosteroid toxicity is frequent and often results in resistance on the part of
patients to reinitiate therapy if they have used it before. Short-term toxicities
observed include moon face (47%), acne (30%), infection (27%), ecchymoses (17%),
hypertension (15%), hirsutism (7%), petechial bleeding (6%), and striae (6%).
Prolonged corticosteroid therapy can result in multiple serious side effects including
hypertension, new onset diabetes mellitus, infection, osteonecrosis, steroid associated
osteoporosis, myopathy, psychosis, cataracts, and glaucoma.

For moderate to severe UC, the preferred initial prednisone dose is 40 mg/day
administered as a single dose. The optimal tapering strategy has not been determined,
but experienced clinicians will typically treat the patient with prednisone 40 mg/day
for 2 to 4 weeks, and then taper by 5 gm/week to a daily dose of 20 mg/day, then
slow the taper to 2.5 mg/week until prednisone is discontinued. For severe UC,
requiring hospitalization, hydrocortisone 300 to 400 mg/day or methylprednisolone
40 to 60 mg/day is used. Five to seven days are required prior to determining
whether the patient has failed steroids.

2.2.1.3 Antibiotics

The lack of efficacy of antibiotics in the treatment of UC and Crohn’s disease is
somewhat surprising given the presumed role of bacteria in the etiology of IBD. One
placebo controlled trial of ciprofloxacin in moderately active UC showed benefit
while another was negative. The addition of intravenous ciprofloxacin to steroids in severe UC was also not of benefit. Oral tobramycin had short-term efficacy in UC but could not maintain remission. In acute severe UC, the combination of tobramycin and metronidazole, oral vancomycin alone, or intravenous metronidazole alone were not added benefit to corticosteroids. Finally, in a small placebo-controlled trial, rifaximin, a nonabsorbed, broad spectrum antibiotic, was not statistically better than placebo in overall clinical outcome in patients with steroid-refractory severe UC, but did have a significant reduction in stool frequency, rectal bleeding, and sigmoidoscopic score compared with placebo. Larger trials are underway.

Antibiotics should not be used without evidence of infection in patients with mild to moderate UC. Although evidence does not support their use in severe UC, in clinical practice the hospitalized patient may receive antibiotics as prophylaxis against bacterial translocation in the severely inflamed colon.

2.2.1.4 Nicotine

Nonsmokers and former smokers have higher rates of UC than current smokers. Also, smokers with UC who stop smoking experience increased severity of disease. The mechanism of this effect is thought to be due to nicotine, but is not completely elucidated. Placebo-controlled trials of Transdermal nicotine patches demonstrated efficacy in achieving clinical remission or improvement at doses of 25 mg/24 hours and 22 mg/24 hours. However, it was not effective for maintenance, although an uncontrolled study suggested that patients who are treated with Transdermal nicotine maintain their response longer than those treated with corticosteroids. Nicotine enemas also demonstrated benefit in uncontrolled trials. The major drawback of nicotine use is the high percentage of side effects, especially in patients who have never smoked before. These side effects include skin irritation, lightheadedness, nausea, vomiting, diaphoresis, central nervous system disturbances, and insomnia.
2.2.1.5 Immunosuppressants

while 5-ASA agents are the first line for induction and maintenance of remission in mild to moderate UC and steroids are used for induction of remission in moderate to severe UC, immune modifier drugs are used to induce remission in steroid-dependent or steroid refractory disease, maintain remission in those patients for whom 5-ASA agents are inadequate, and as salvage therapy in severe disease refractory to steroid therapy.

2.2.1.6 Azathioprine/6-Mercaptopurine

6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are purine antimetabolite drugs demonstrated to be effective for the induction and maintenance of remission in UC and have proven steroid-sparing effects. The efficacy of 6-MP was recognized as early as 1962. Though some controlled studies of AZA versus placebo and AZA versus sulfasalazine in the treatment of acute attacks of colitis found no significant benefit, others found that AZA use resulted in improved disease activity, a decreased need for steroids, and prolonged rates of remission. Multiple uncontrolled studies confirmed the benefits of AZA/6-MP.

Effective doses of AZA are 2.0 to 3.0 mg/kg/day and of 6-MP are 1/0 to 1/5 mg/kg/day and may take up to 17 weeks to take complete effect. Though some physicians begin at low doses and titrate upwards, our practice is to begin at full dose with careful monitoring of the complete blood count. There is no role for intravenous loading of AZA in severe UC. Thiopurine S-methyltransferase (TPMT) phenotype of genotype can aid in determining safety and optimal dosage of AZA/6-MP. Low to intermediate levels of TPMT are associated with leucopenia in rheumatoid arthritis and with Crohn’s disease. Based on these observations, it is recommended that patients with normal TPMT activity receive standard doses of AZA or 6-MP. Patients with intermediate activity should receive 50% of the standard dose and those who have no TPMT activity should not be treated with the drug. The use of
metabolite levels (6-TGN [thioguanine nucleotides] and 6-MMP [6-methylmercaptopurine]) to gauge optimal dosing of AZA/6-MP is controversial. Though two studies supported its use, three others failed to demonstrate a consistent relationship between clinical efficacy and erythrocyte 6-TGN concentrations.

Allergic reactions occur in 5% of patients taking AZA or 6-MP and include pancreatitis, fever, rash, malaise, nausea, diarrhea, and some cases of hepatitis. Nonallergic reactions include bone marrow suppression leading to leucopenia, anemia or thrombocytopenia, opportunistic infection, and hepatitis. Lymphoma does not appear to be increased above what is expected in IBD, though there may be an increase in Epstein-Barr virus associated lymphomas in patients treated with AZA/6-MP.

2.2.1.7 Methotrexate

Methotrexate (MTX) has demonstrated benefit for the induction and maintenance of remission in Crohn’s disease, however, its benefit in UC is not well established. Uncontrolled data have shown response in small series of patients with UC. The only controlled trial in UC was by some of the clinicians and associates, which compared oral MTX 12.5 mg/week with placebo group in remission and relapse rates. A recent study reported on patients with steroid-dependent or steroid-resistant active UC. Then patients were intolerant or resistant to AZA and were switched to MTX 12.5 mg IM/week. Six of 10 (60%) achieved clinical remission, 40% achieved clinical response, and 20% subsequently relapsed. Available data suggest that AZA/6-MP should be the first choice for maintenance and steroid sparing in UC, but MTX can be tried in those who are intolerant or resistant to AZA/6-MP. Our usual starting dose is 25 mg SQ/ week, though once remission is achieved, 15 mg SQ/week can be used for maintenance.

MTX should always be given with folic acid 1 mg per day. Use in patients who are diabetic, obese, use excessive alcohol, or have known liver abnormalities is
contraindicated. MTX is teratogenic and should not be used in men or women attempting conception. Increased serum transaminases and hypersensitivity reactions such as rash and pneumonitis can sometimes be seen.

2.2.1.8 Cyclosporine

Cyclosporine (CSA) is a calcineurin inhibitor that is used as salvage therapy for induction of remission in severe, steroid-refractory UC that would otherwise require colectomy. There are four randomized trials that have demonstrated the efficacy of CSA in severe UC. The first research found that 9/11 (82%) steroid-refractory UC patients had clinical response with 4 mg/kg/day of CSA in combination with intravenous steroids, versus none of placebo-treated patients on intravenous steroids alone. Two other controlled studies suggested that CSA alone at a dose of 4 mg/kg/day without steroids is effective in inducing remission in severe UC. Finally, a study by the researcher found that 2 mg/kg/day of CSA is equivalent to 4 mg/kg/day in achieving response in severe UC.

Patients who respond to 4 mg/kg/day of IV CSA are continued on the drug for 7 to 10 days. The target whole blood CSA level is 300 to 350 ng/ml for the 4 mg/kg/day dose or 150 to 250 ng/ml for the 2 mg/kg/day dose. They are then converted to oral CSA at a dose of 8 mg/kg/day or twice the IV dose in hospital. The desired CSA level on oral dose is 150 to 300 ng/ml. unfortunately, 45% of patients on oral CSA alone will require colectomy at 6 months. This can be decreased to 20% by the addition of 6-MP/AZA at discharge from the hospital. Patients are also continued on prednisone, which is tapered during outpatient follow-up. This regimen of triple immunosuppressive therapy with CSA, 6-MP/AZA, and prednisone can lead to significant infectious complications. For this reason, trimethoprim/sulfamethoxazole are added for prophylaxis. One uncontrolled study suggested that patients responding to IC/CSA can be started on oral AZA without oral CSA, and prednisone can be tapered accordingly, however, the colectomy rate was 41%.
An oral, micro emulsion form of CSA (Neoral) has been developed which has increased oral bioavailability and improved absorption from the small bowel. The pharmokinetic parameters of CSA micro emulsion in patients with IBD appear to be similar to those of healthy volunteers. Three small series have described efficacy of oral microenurism CSA in severe UC, though larger controlled trials are needed.

In a report from Mount Sinai Hospital on 111 IBD patients treated with CSA, the most frequent adverse events were paresthesias (51%), hypertension (43%), hypertrichosis (27%), renal insufficiency (23%), infections (20%), gingival hyperplasia (4%), seizures (3%), death (2%), and anaphylaxis (1%). In a similar report from the University of Chicago on 74 patients with IBD treated with CSA, 54% experienced adverse events including severe events such as pneumocystis carinii pneumonia in two patients, abdominal abscess, grand mal seizure, mycotic aneurysm, and renal insufficiency.

CSA in severe UC is definitely effective, but its side-effect profile and tangible long-term failure rate must be discussed in depth with the patient debating colectomy versus salvage medical therapy. Also, patients who are not tolerant of AZA/6-MP are not good candidates for CSA therapy, as CSA alone has a high colectomy rate over time. Side effects may be decreased by using lower doses of IV CSA at 2 mg/kg/day, using antibiotic prophylaxis, or avoiding triple therapy with oral CSA, AZA and prednisone.

2.2.1.9 Tacrolimus

Tacrolimus is a calcineurin inhibitor like CSA. Controlled trials in severe UC have not been conducted to date, but multiple case series suggest efficacy. The first study described a 69% clinical response rate in 13 patients with steroid refractory UC. However, at 1 year, only 38% of patients avoided colectomy. Three case series note salvage therapy with Tacrolimus in steroid-resistant or steroid-dependent UC as well as in a patient with toxic mega colon. One trial compared intravenous to oral
Tacrolimus in 38 patients with refractory UC. Oral and IV dosing was equivalent. Eighteen of 38 patients (47%) improved within 14 days. Thirty-five of 38 patients (92%) avoided colectomy at 28 days, but at 2 years, the colectomy rate was 50%.

The dose of oral Tacrolimus is 0.1 to 0.2 mg/kg/day given in divided doses twice daily. The serum trough levels are 4 to 6 ng/ml. Patients should be monitored closely for evidence of infections and trimethoprim/sulfamethoxazole prophylaxis should be used. Side effects include transient renal insufficiency, tremor, paresthesias, hyperkalemia, and hypertension. These often resolve with lowering of the dose.

### 2.2.1.10 Infliximab

Infliximab is a chimeric monoclonal antibody to tumor necrosis factor-α (TNF), a key inflammatory cytokine. While infliximab has made a dramatic impact on the treatment of Crohn’s disease, its role in UC is not clear. The researcher reported 11 patients in a controlled trial of infliximab in severe, steroid-refractory UC. Four to eight patients (50%) who received infliximab had a clinical response, although one subsequently required colectomy. Two small case series report response in severe UC, but a larger randomized controlled trial was negative. In this latter trial, patients with severe, steroid-refractory UC were randomized to infliximab 5 mg/kg or placebo at weeks 0 and 2. After 6 weeks, remission was achieved in 8/22 infliximab patients and 6/20 placebo (not significant). A controlled trial of infliximab in nonsteroid-refractory patients randomized patients to either infliximab 5 mg/kg at 0.2, and 6 weeks or intravenous prednisolone at 1.5 mg/kg daily for 2 weeks followed by a taper. Five of 6 patients receiving infliximab and 6/7 patients receiving steroids had a response. The two agents appear to be equivalent in this small study.

Clinical experience and a placebo-controlled trial suggest that infliximab is not effective in steroid-refractory UC. This is further supported by a retrospective analysis of 27 patients with active UC who received infliximab. While 44% of all UC patients achieved remission and 22% had a partial response, steroid-refractory
patients were less likely to respond when compared with steroid-responsive patients (33% vs 83%; p= 0.026). Infliximab should not be used in severe, steroid-refractory UC. Evidence for its use in steroid-responsive disease is anecdotal at best and controlled studies are needed.

2.2.1.11 Experimental Agents

2.2.1.11.1 Heparin

Thrombotic events associated with UC and histologic evidence of micro vascular thrombosis on colon biopsy suggested that anticoagulation may be an effective therapy for UC. Uncontrolled studies did find unfractioned heparin to be of benefit, but small controlled studies comparing unfractioned heparin to corticosteroids had mixed results. Larger, placebo-controlled trials of low-molecular-weight heparin in studies of 100 patients and 138 patients, respectively, found no significant benefit over placebo. Heparin is not effective for the treatment of UC but does appear to be safe with no increased risk of gastrointestinal bleeding, should the need for anticoagulation for other reasons arise in these patients.

2.2.1.11.2 Biologics: Cytokines and Antibodies

Investigational agents with preliminary reports of efficacy include vepolimomab (monoclonal antibody [mAb] to vascular adhesion protein-1); interleukin-2 (IL-2) antagonists such as basiliximab, which may increase response to steroids in steroid resistant UC; anti-CD3 antibodies, such as visilizumab, which has shown preliminary efficacy in steroid-resistant UC; antibody to α4β7, such as MLN-02, which mediates recruitment of lymphocytes to the gut and demonstrated safety and efficacy in a controlled trial in patients with active UC; and interferon-β, which showed some clinical response in patients with steroid-refractory UC in a phase II, placebo-controlled trial. Multiple other agents exist, but for all new agents, while preliminary
results are exciting, randomized controlled trials are needed before widespread use is initiated.

2.2.1.11.3 Leukocytapheresis

Watson G. (1961) has observed in one novel technique for the treatment of severe UC is Leukocytapheresis. Based on the theory that inflammation and damage to the colonic mucosa are caused by products of activated granulocytes, monocytes, and macrophages, an extracorporeal Leukocytapheresis column (LCAP) was developed to remove these cells from the peripheral circulation, with reported efficacy in UC. A randomized controlled trial in 76 active UC patients reported that addition of LCAP to corticosteroids improved clinical response with a reduction in steroid dosage. These results were corroborated by a recent randomized trial from the same group showing that LCAP was more effective than sham perfusion (80% vs 33%; \( p < 0.05 \)) in eliciting clinical response in patients with active UC.

2.2.1.12 Ancillary Medical Measures:

Anticholinergics may be of some value in reducing abdominal pain and lessening the severity of the diarrhea. Propantheline bromide (probanthine) appears to be a suitable agent for this purpose in a dose of 15 mg. three or four times a day. It should not be given by mouth if it is being given parenterally to aid in the retention of a rectal drip. There is the possibility that large doses of Anticholinergics may predispose to the dangerous complication of acute dilatation of the colon.

Antibiotics have only a minor role to play in the treatment of ulcerative colitis. Broad spectrum antibiotics given by mouth are best avoided as they are themselves liable to cause a dangerous enterocolitis. At the height of a severe attack a broad spectrum antibiotic such as tetracycline 250 mg. four times a day can be given in the intravenous infusion for a maximum period of five days.

Sedatives are useful in relieving some of the patient’s anxiety and in increasing the chance of his being able to get a good night’s sleep.
2.2.1.13 Medical Measures which are Best Avoided:

It is best not to give broad spectrum antibiotics by mouth. As mentioned above they are themselves apt to provoke a dangerous enterocolitis. I have seen a number of patients with ulcerative colitis in remission put into an acute attack by the administration of a broad spectrum antibiotic for some other trivial disease.

The use of opium and of codeine in large quantities in the hope of checking the diarrhea is usually futile. These agents are not very effective in ulcerative colitis, and they are sometimes given in such large quantities that they are opt to befuddle the patient and make the clinical picture obscure.

Oral iron is best avoided during the attack. It may cause an exacerbation of the diarrhea, and in any event there is evidence that iron is poorly utilized by the bone marrow during an acute attack of ulcerative colitis. If there is anemia the correct treatment is blood transfusion. When the attack is over it is wise to replenish the body stores of iron either by a course of parenteral iron or by a small oral dose over a period.

2.2.1.14 Intensive Medical Management:

When a patient is admitted severely ill with an uncomplicated attack of ulcerative colitis it has become our practice at Oxford to give immediately a five-day intensive course of medical treatment. Nothing is given by mouth other than sips of water. An intravenous drip is maintained throughout the five-day period, with saline or glucose saline containing potassium supplements and with Aminosol plus fructose and alcohol. Corticosteroids are given in the intravenous saline drip, usually as hydrocortisone, hemisuccinate sodium 200-300 mg. a day or as prednisolone 21-phosphate 40-60 mg. a day. Tetracycline in a dose of 250 mg. four times a day is also given in the intravenous drip. A rectal drip of hydrocortisone hemisuccinate sodium 100 mg. is given morning and evening.

Rapid improvement frequently occurs with this regimen. Assuming that this is so, treatment is switched to oral administration at the end of the five-day period. If
improvement does not occur, the question of emergency colectomy must be considered.

It is also our practice to resort to a five-day intensive course if a patient admitted in a moderately ill state shows no favorable response to oral treatment after about a week.

No controlled therapeutic trials have been made on this approach to the treatment of severe attacks of ulcerative colitis, but our clinical impression is that it is a useful way of obtaining rapid improvement in a large proportion of the patients. It is, of course, essential to satisfy oneself that the patient is not suffering from a dangerous complication requiring emergency surgery—of which perforation of the colon is the prime example—before embarking on this intensive medical therapy.

2.2.1.15 Management of the Less Severe Attacks:

Moderately severe attacks are managed along the same lines as a severe attack, but not all the general medical measures will be required. For example, blood transfusion is often unnecessary, and dehydration and electrolyte depletion may not be pronounced.

Mild attacks can almost all be checked by treatment on an outpatient basis. The sooner treatment begins the better the prospect of aborting the attack. My personal preference is to use immediately a combination of oral and topical corticosteroids. The usual outpatient treatment consists in prednisolone 5 mg. four times a day by mouth and hydrocortisone hemisuccinate sodium 100 mg. by rectal drip nightly. This regimen is continued for a month even if there is a rapid response. Assuming that the patient is then symptom-free, the oral prednisolone is tailed off over the course of the next few weeks, but the rectal drip is continued for about three months. If the patient is not already on sulphasalazine, he is put on this in a maintenance dose of 0.5 g. four times a day, unless there are specific contraindications; for example, it may be known that he has previously developed unpleasant side-effects or complications with this drug.
If the patient does not show prompt improvement with the combined oral and local corticosteroid treatment he should be admitted without delay as an impatient, so that treatment can be given with bigger does along the lines already covered. By strictly limiting the dosage of corticosteroids when dealing with outpatients, we have found that this form of treatment can be used extensively with negligible risks.

One practical point is worth emphasis. Some physicians take up a “wait and see” attitude when a patient with ulcerative colitis develops a minor relapse. I regard this as mistaken, for some of these minor relapses will evolve into severe attacks unless active measures are taken to abort them. The risks of short-term corticosteroid therapy are trivial in relation to the risk of doing nothing and taking the chance of a severe attack developing. Consequently, every patient with ulcerative colitis should be encouraged to report without delay at the first signs of colitis symptoms. If sigmoidoscopy shows active inflammation a course of treatment should be given no matter how slight the symptoms. The vigorous application of this simple rule is one of the most important ways of making the best use of our present medical methods.

2.2.1.16 Psychotherapy:

Some physicians regard ulcerative colitis as a psychosomatic disease in the most strict sense of the term—namely, as an illness in which an emotional disturbance is the primary event and the diseased organ is the somatic consequence. Other physicians regard psychological factors as important in the etiology of the disease without going as far as regarding them as the sole cause. Others are skeptical of the role of psychological factors in causation and regard any emotional disturbances as by-products of a serious organic disease.

The view that psychological factors are of importance in causation rests upon two separate types of observation. On the one hand, a close temporal relationship can often be established between an emotional event and the onset of ulcerative colitis. The loss, real or imagined, of the patient’s mother, or of some other person acting as a substitute mother, has sometimes been regarded as the most frequent precipitant of ulcerative colitis. On the other hand, personality profiles of patients with ulcerative
colitis have been claimed to show that the patients do not represent a random sample of the general population, but are often excessively neat and tidy, shy, unaggressive, and inclined to bottle up their feelings rather than express them overtly.

It is natural that some of the physicians who regard psychological factors as of cardinal importance in the genesis of ulcerative colitis should also regard psychotherapy as equally important in its treatment. Strong claims for the beneficial effects of this approach to management have been made by a few enthusiasts, but, in general, the physicians and surgeons with extensive experience of ulcerative colitis regard psychotherapy as a secondary approach to treatment.

This is not to underestimate the necessity of taking psychological factors into account when dealing with patients with ulcerative colitis. However skeptical one may be about the role of psychological factors in the initiation of the disease, there can be little doubt that once the disease is established an emotional disturbance may trigger off a relapse. In addition, the disease is one which, when it takes a severe form, is debilitating and disagreeable; patients so afflicted require much care as human beings. As this is an illness which is likely to react on other members of the family, attention to human and social factors should ideally extend outside the patient himself. The services of a psychiatrist and of a medical social worker are often highly advantageous, but it seems best to regards them as complementary to, and not a substitute for, ordinary medical and surgical care.

2.2.2 Nutritional Management:

Antia F.P. (1998), Sharma R. & Eiden K.A. (2003) has commonly observed that ensuring good nutrition is an important part of managing Ulcerative Colitis (UC). People with UC may be at risk for developing malnutrition and nutrient deficiencies, which makes it more difficult for the body to heal and fight infection. Malnutrition may also cause you to feel more fatigued. There are several reasons that people with UC may be at nutritional risk. These include the following:

- Decreased food intake due to decreased appetite, pain, diarrhea, or other symptoms (or fear of these symptoms)
• Increased need for calories, protein and some vitamins and minerals
• Diarrhea or other fluid losses can lead to dehydration if not replaced
• Preexisting dietary restrictions (which may or may not be necessary)

2.2.2.1 Nutrition Assessment in Inflammatory Bowel Disease

Factors Affecting Nutritional Status in the Patient with IBD

There are many factors that alter nutrient intake in the patient with IBD. Nutrition abnormalities can be a result of malabsorption. Decreased food intake, medications and/or intestinal losses. These deficiencies will differ between individual activity and specific nutrient absorption found at these sites. For a list of factors precipitation nutritional demise in patients with IBD, see Table 1.

Table 1 Factors Altering Nutritional Status in Patients with IBD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased nutrient intake</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Fear of eating</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, abdominal pain, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Restrictive diets</td>
<td></td>
</tr>
<tr>
<td>Side effects of medications</td>
<td></td>
</tr>
<tr>
<td>Appetite suppression, taste changes</td>
<td></td>
</tr>
<tr>
<td>Oral aphthous ulcerations</td>
<td></td>
</tr>
<tr>
<td>Protein losses from inflamed, ulcerated mucosal</td>
<td></td>
</tr>
<tr>
<td>Increased needs for healing</td>
<td></td>
</tr>
<tr>
<td>Surgical resections</td>
<td></td>
</tr>
<tr>
<td>Increased vitamin and mineral needs</td>
<td></td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td></td>
</tr>
<tr>
<td>Blood loss</td>
<td></td>
</tr>
</tbody>
</table>
No single indicator is available to determine an individual’s nutritional status; assessment requires a nutritional history, physical exam, objective laboratory parameters and clinical judgment. Subjective global assessment (SGA), developed originally for use in oncology patients, is a useful tool for screening an IBD patient. Using SGA, patients are categorized into one of three stages: well nourished, moderately malnourished or severely malnourished. SGA takes into account history of weight changes, food intake, gastrointestinal (GI) symptoms and functional capacity SGA, coupled with physical exam. Provides clinicians with an indication of the patients’ nutrition risk and need for intervention.

Further evaluation of nutrition risk can involve the use of body mass index (BMI). However, one measured weight cannot provide a thorough picture of risk. In addition, a normal appearing BMI does not necessarily correlate with an adequately nourished patient. One has to establish if the weight has significantly changed, over what period of time and if weight loss was intentional or not. A very low BMI or significant change in BMI requires more immediate nutrition intervention.

Clinicians often use albumin as a marker of nutritional status. However, in the case of a hospitalized or sick patient, a low albumin reflects an acute or chronic inflammatory process such as infection, trauma of cancer. The IBD patient often falls into this category. During the inflammatory process, albumin synthesis is decreased, degradation is increased and transcapillary losses from the plasma compartment are increased. IBD patients often have losses from their GI tract that can also impact serum levels. A serum should not guide the clinician in the decision to initiate nutrition support. Although many patients with low albumin have poor nutritional intake, it is unlikely that this is responsible for their low albumin levels. Albumin levels reflect the metabolic response to stress and therefore will not normalize in these patients until the inflammatory process is versely. A normal albumin level in a patient without intake for an extended period of time does not always correlate with adequate nutritional stores as demonstrated in the case of patients with anorexia nervosa.
2.2.2.2 Macronutrient requirements in Inflammatory Bowel Disease

2.2.2.2.1 Calories

There are many equations available to estimate energy requirements. However, validation with clinical outcome is still wanting. Recent studies have shown resting energy requirements are not increased in patients with Ulcerative colitis. BMI can be used for estimating caloric requirements although needs must be reassessed over time. (Table 2). The use of BMI to calculate energy needs is based on the theory that the lower the BMI, the less adipose, more lean, metabolically active tissue present. Caloric requirements are higher per kilogram body weight in patients with lower BMI’s, however; some patients with a high BMI are very active and possess greater amounts of lean tissue (i.e., weight lifters). A word of caution however, any patient with a significant weight loss should be started on a refeeding caloric level (20-25 kcal/kg) and monitored before advancing to a higher caloric goal.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Energy Requirements (kcal * kg⁻¹ * d⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>36-45</td>
</tr>
<tr>
<td>15-19</td>
<td>31-35</td>
</tr>
<tr>
<td>20-29</td>
<td>26-30</td>
</tr>
<tr>
<td>&gt;30</td>
<td>15-25</td>
</tr>
</tbody>
</table>

Note: The lower range within each category should be considered in a critically ill patient, unless he or she is depleted in body fat, to decrease the risk of hyperglycemia and infection associated with overfeeding.
2.2.2.2 Protein

Patients with IBD may have increased protein needs due to losses from inflammation of the intestinal tract, catabolism when an infection is present (i.e., abscess) and possibly for healing if patient requires surgery. Protein needs are assessed based on disease status and body weight. The recommended daily allowance (RDA) for protein is 0.8 g/kg actual weight. The majority of IBD patients free from renal disease require approximately 1.0-1.5 g/kg body weight. Protein may need to be restricted in renal failure patients who are not receiving dialysis. Patients on either hemodialysis or peritoneal dialysis require 1.2-1.5 g/kg body weight to meet needs and to replace the protein lost in the dialysate. Ideal body weight can be used to prevent provision of excess protein to patients who are obese.

2.2.2.3 Vitamin and Mineral Issues in Inflammatory Bowel Disease:

Vitamin and mineral deficiencies in IBD have been well documented. Although serum levels of some nutrients may be reported as low, interpretation of these findings and consequent treatment guidelines are not well established. There are no gold standards for measurement in clinical practice for many of these nutrients. Table 3 provides information on signs and symptoms of vitamin/mineral deficiencies commonly found in the patient with IBD based on clinical practice and research available. Treatment recommendations that may correct deficiency states are also listed.
Table 3
Vitamin and mineral requirements and assessment and treatment of deficiencies

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Signs or symptoms</th>
<th>Recommended Daily of a deficiency replacement Requirements (Oral Dose)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>15 mg</td>
<td>Dry, flaky skin, peeling Palms, diarrhea, mental Status changes</td>
</tr>
<tr>
<td>Iron</td>
<td>10-15 mg</td>
<td>Microcytic anemia, Fatigue</td>
</tr>
<tr>
<td>B12 (Coabalmin)</td>
<td>3 mcg</td>
<td>Megaloblastic anemia, Paresthesias, ataxia, Diarrhea, mental status Changes</td>
</tr>
<tr>
<td>Folate</td>
<td>400 mcg</td>
<td>Sore mouth, glossitis, Diarrhea, forgetfulness, Megaloblastic anemia</td>
</tr>
<tr>
<td>Calcium</td>
<td>800-1500 mg</td>
<td>Osteopenia, osteoporosis, Tetany</td>
</tr>
<tr>
<td>Magnesium</td>
<td>400 mg</td>
<td>Nausea, muscle weakness, Arrhythmia’s, confusion</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400 IU</td>
<td>Rickets, osteomalacia, Bone pain, muscle weakness, tetany</td>
</tr>
</tbody>
</table>

* Amounts are general guidelines and should be adjusted based on individuals needs with ongoing assessment as to the cause (i.e., malabsorption)
2.2.2.3 Vitamins:

2.2.2.3.1 Vitamin B12:

Vitamin B12 status can be altered in those patients who have had surgical resections of the stomach (intrinsic factor production) and/or the terminal ileum (site of absorption). Although intra-muscular (IM) replacement is the treatment of choice for most clinicians, oral supplementation is possible with higher doses of synthetic B12. A nasal gel is also now available (Nasocobal) that can be used in place of monthly IM injections. Cost difference between oral, IM and nasal doses are found in Table 4.

<table>
<thead>
<tr>
<th>B12 Formulation</th>
<th># Doses per Month</th>
<th>Average Cost Per Month *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>4</td>
<td>$34.80 (500 mcg dose)</td>
</tr>
<tr>
<td>Nasocobal</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong><a href="http://www.nastech.com/nasocobal">www.nastech.com/nasocobal</a></strong></td>
<td>(888) 514-5208</td>
<td></td>
</tr>
<tr>
<td>IM injection</td>
<td>1</td>
<td>$0.79 (1000 mcg dose)</td>
</tr>
<tr>
<td>(Does not include cost of Syringes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule</td>
<td>30</td>
<td>$0.76 (1000 mcg dose)</td>
</tr>
</tbody>
</table>

* Wal-Mart March 2003

Serum methylmalonic acid (S-MMA) is a more sensitive indicator of Coabalmin deficiency than serum vitamin B12. Elevated concentrations of S-MMA represent a metabolic change that is very specific to B12 deficiency making it the preferred indicator of B12 status. Homocysteine is also an indication of pending B12
deficiency, unfortunately, it is also affected by B6 and folate status, is commonly elevated in the elderly, and therefore, it has poor specificity to serum B12.

There are four stages of B12 deficiency. In stage 1 and 2, plasma and cell stores become depleted. Increased levels of S-MMA and Homocysteine are found in stage 3 with clinical signs becoming apparent in stage 4 (macroovalocytosis, increased mean corpuscular volume (MCV) and decreased hemoglobin). Studies have shown 60% of vegetarians have stage 3 deficiency with recommendations to monitor B12 status in this group of patients closely. Use of S-MMA for general practice diagnosis of B12 deficiency may promote over treatment with B12 and may not be readily available at most laboratories. Use of S-MMA as a screening tool would not be recommended. Although may be worthwhile in high-risk populations. S-MMA is strongly associated with serum creatinine levels. Yet it is unclear the extent to which the increased levels are attributed to impaired renal function versus impaired Cobalamin metabolism.

2.2.2.3.2 Folate:

Some medications used to treat IBD, such as Methotrexate, a folate antagonist, and sulphasalazine, which blocks folate absorption, increase folate requirements. Good sources of folate (i.e. green leafy vegetables, legumes) can be difficult to tolerate for some IBD. Patients and therefore a supplement may be beneficial. The best indicator of folate status is red blood cell folate as it is only taken up by the developing erythrocyte in the bone marrow. In patients on routine folate supplementation, beware of a potentially masked B12 deficiency and monitor periodically. Folate supplementation may also be protective against colon cancer.

An increased Homocysteine level has been identified as a risk factor for thrombosis, atherosclerotic cardiovascular disease and stroke. Research has found hyperhomocysteinemia to be significantly more common in IBD compared to healthy controls and is associated with lower levels (but not necessarily deficiency states) of vitamin- B12 and folate.
2.2.2.3.3 Calcium and Vitamin D

Long-term steroid use leads to accelerated bone loss with resultant Osteopenia or osteoporosis. A decreased intake of dairy foods as a result of lactose-restricted diets can further that loss without attention to calcium and vitamin D status. Patients with IBD have a reduction in bone mineral density that is multifactorial in nature. Risk factors include: corticosteroids, vitamin D deficiency, malabsorption, malnutrition, hypogonadism, and systemic inflammation. Of note, in IBD, continuous, higher dose (.75 mg/d) corticosteroids as compared to alternate day and lower dose treatment have been associated with a greater loss in bone mineral density. Dual energy x-ray absorptiometry (DEXA scan) is recommended to evaluate bone density. Assessment of adequate calcium and vitamin D intake is important in all patients with IBD with supplementation if the diet is found deficient. One tablet of Oscal 500 plus vitamin D given 2 to 3 times per day can meet requirements providing 1000-1500 mg calcium and 400-600 IU of vitamin D. Patients with osteoporosis may need more aggressive therapy with a biphosphonate agent. For more information on calcium and vitamin D supplements, see February 2003 Practical Gastroenterology article on lactose intolerance.

There is evidence that “prednisone induces a state of vitamin D resistance” which increases parathyroid hormone levels and calcium losses. Patients may need a higher dose of vitamin D to inhibit this process with up to 50,000 IU every 2-4 weeks, although large amounts of vitamin D are not recommended for long term use in patients with a functional GI tract. In patients with severe malabsorption 2000-4000 IU of vitamin D per day may be needed to achieve normal serum 25- hydroxyvitamin D levels. In general, the daily requirement of 400 IU per day would be recommended for the IBD patient at risk for deficiency.
2.2.2.4 Minerals:

2.2.2.4.1 Zinc:

In both UC and Crohn’s disease, patients can have excessive stool losses or develop high output fistulas that may require supplemental zinc. It has been estimated that up to 15 mg can be lost per liter of stool output. There is no gold standard applicable in clinical practice for the measurement of zinc status. The majority of research has shown decreased serum levels in Crohn’s patients versus controls though no actual symptoms of deficiency were detected. This can be referred to as an “apparent” zinc deficiency meaning other things such as inflammatory stress or low albumin levels (zinc is transported in part by albumin) are responsible for low serum levels. At our institution, there have been cases of patients with short gut developing clinical signs of deficiency exhibiting peeling of palms and soles of feet with resolution of symptoms with the addition of extra intravenous zinc (up to 15 mg per day) provided in total Parenteral nutrition.

2.2.2.4.2 Iron:

Blood losses, more prevalent in UC, can lead to iron deficiency anemia. This can be difficult to correct with diet alone. Iron supplements and iron rich foods may have enhanced absorption when a source of vitamin C is ingested at the same time. Although larger doses are often used. Only 25-50 mg of vitamin C is necessary to increase iron bioavailability. This can be achieved by taking iron with 2-3 ounces of a vitamin C containing beverage or a portion of the standard 250 mg Vitamin C Tablet.

2.2.2.4.3 Magnesium:

Magnesium can be a concern especially with patients experiencing increased intestinal losses as is the case in many IBD patients. Especially those with short bowel syndrome. A recent study found a correlation between a low serum magnesium and risk for lower bone mass density.
Magnesium can be repleted via the enteral or Parenteral route. The pH of the stomach to ileum, GI transit time and the fat content of a meal can affect the degree of intestinal magnesium absorption. Supplementation with large amounts of enteral magnesium may cause diarrhea, especially if given over a short period of time. Although magnesium oxide and magnesium hydroxide have a greater percentage of magnesium per tablet than magnesium gluconate (60%, 41% and 5.4% respectively), magnesium gluconate has a higher degree of solubility, making it a better choice for intestinal supplementation.

2.2.3 Medications:

Medications used in the management and treatment of IBD may have several nutritional implications. Steroids, commonly used in IBD patients, can lead to bone disorders as discussed above and may also lead to diabetes. Important GI side effects of Flagyl include decreased appetite, metallic taste and dyspepsia. Cholestyramine can bind fat-soluble vitamins (A, D, E and K) as well as interfere with folate and magnesium absorption. Given the many reasons for nutrient deficiencies in IBD, in our institution, patients are advised to take a multivitamin/mineral complex daily. There are, however, no controlled trials to support this practice. Forvia, a product formulated and marketed for the patient with IBD is available via the Internet. This product contains water-miscible forms of fat-soluble vitamins with increased amounts of vitamin D, vitamin K and vitamin E, vitamin B12 and zinc. Forvia does not contain magnesium due to its potential cathartic side effect. A multivitamin supplement or prenatal vitamin will meet the needs of most IBD patients and are less expensive than specialized formulations, such as ADEK or Forvia may be beneficial, however, there are no clinical trials demonstrating superiority over standard for mutations in this patient population.

2.2.4 Oral Diets in Inflammatory Bowel Disease:

Joshi S. said that To date, no special diet has been found to be efficacious in the treatment of IBD, patients with IBD should be encouraged to follow a normal, healthy diet as tolerated. In some patients, however, the diet may need to be tailored
to meet individual needs during the course of treatment based on symptoms and patient preferences. Smaller, frequent meals and use of oral liquid supplements can also be used. Juice based products such as Boost Breeze (www.meadjohnson.com) and Enlive (www.ross.com) are new to the market. Formulas developed and marketed for use during Crohn’s or UC flares are often elemental or semi-elemental and have low compliance rates due to cost, taste, smell and texture.

2.2.4.1 Fiber:

Low (and occasionally high) fiber diets are frequently recommended in patients with IBD, although prospective randomized studies have not shown a clear benefit. Low fiber diets can limit short chain fatty acids, the preferred fuel for the colonocyte. There is often confusion with regards to the difference between low fiber and low residue diets. Low residue diets limit fiber as well as any other food known to leave a residue in the GI tract (such as milk products, prune juice, etc). Low fiber diets may be beneficial for several conditions (i.e. strictures, diverticulitis), not so for a low residue diet. No difference in complications was seen between a low residue diet (defined as exclusion of legumes, whole grains, nuts, all fruits and vegetables with the exception of ripe bananas and skinned potatoes) and a regular diet in Crohn’s patients. “Diet as tolerated” is still the mainstay recommended to patients with IBD.

2.2.4.2 Lactose:

Milk intolerance in IBD patients is estimated to be between 10% and 20%. However, these studies did not take into account ethnicity. The prevalence of lactose intolerance in UC is no different than the normal population. Evidence suggests a higher prevalence of lactose intolerance beyond ethnic predictions in Crohn’s patients relating to the disease location.

Lactose restrictions should only be employed in patients exhibiting symptoms of cramping pain, gas and diarrhea after consuming dairy products. This may be difficult to distinguish in patients with active IBD. However, a trial of a lactose restricted diet with lactase and calcium supplements may be worthwhile. Lactose free milk can contain up to 50% of daily requirements for calcium per serving compared
to 30% of needs in regular milk. As lactose intolerance is dose-dependent. Most patients can tolerate up to one cup of milk with a meal without the need for lactose supplementation.

### 2.2.5 Strictures/ Luminal Narrowing/ Ostomies:

In IBD patients with strictures it may be prudent to avoid high fiber, nuts, seeds, mushrooms, popcorn, celery and fruit/vegetable skins. It is especially important that patients chew their foods well if strictures are present. Finally, some patients may need to rely on liquids as the sole source of nutrition if strictures or narrowing do not allow passage of normal foods.

At our institution patients with new ileostomies are instructed to avoid the high fiber foods listed above for a period of 2-4 weeks to allow post-op swelling to subside. Fiber-containing foods are added back slowly beginning with water-soluble fibers (oatmeal, bananas, rice and applesauce) followed by insoluble fibers (wheat, bran, corn or nuts) as tolerated. There is no data available to support undigested food in their effluent. Although this may be distressing to patients, from a clinical standpoint, no negative outcomes have been reported. Finally, the following categories are reported (based primarily on surveys) to be associated with an increase in odor, effluent or gas respectively:

**Odor:** onion, eggs, fish, cabbage/cabbage family, legumes, cheese

**Increased effluent:** Tokay grapes, dried fruits, baked beans, fresh peaches and strawberries, prune juice, coconut, nuts, seeds or kernels, cabbage, celery, bamboo shoots, corn, lettuce, milk

**Gas:** carbonated drinks, legumes, cabbage, onions, broccoli, cucumber, spinach

Patients with ileostomies may require additional fluid and sodium in order to maintain a urine output > 1200 mL/day. This is especially important to those living in hotter climates or in the summer months. The nutritional challenges presented by the patient with short bowel syndrome will be addressed in a future article in the series.
2.2.6 Medium Chain Triglycerides:

Medium chain triglycerides (MCT) are often suggested for use in patient’s fat malabsorption. Unfortunately, they are quite expensive and are not well received by patients in general. It may be more palatable (and less expensive) to incorporate MCT in the form of an MCT containing liquid supplement vs MCT oil alone. It is also important when using MCT oils not to exceed the threshold dose for patients with ileitis or an extensive resection of the small intestine, as osmotic diarrhea may be a result. A dose of MCT oil up to 50 g/day (8 tablespoons) can be introduced in small amounts over the course of the day with meals. Ingestion of large amounts of MCT oil will further decrease the absorption of long chain triglycerides. Of note, because MCT only include fats with carbon chains of C10 or less, they do not contain essential fatty acids. Table 8 and 9 contains a product list and cost comparison of some of the MCT oils and MCT containing products on the market. The MCT containing products listed can be mixed with sorbets or sherbets to further increase calories and improve palatability.

2.2.7 Nutrition Support in Inflammatory Bowel Disease:

2.2.7.1 Enteral Nutrition:

The use of enteral nutrition support in treating IBD has been evaluated in many prospective randomized controlled trials. Studies to date have shown steroid therapy to be more effective in obtaining remission than enteral nutrition in patients with Crohn’s disease. No difference has been observed between elemental (nitrogen in the form of peptides or protein hydrolyzates) and polymeric (nitrogen in the form of whole proteins) formulas. Table 7 provides a cost comparison of some of the elemental/oligomeric formulations marketed for IBD versus isotonic, polymeric formulas. Further studies are needed to determine whether specialized nutritional therapy may be helpful in preventing relapse of disease and decreasing steroid requirements in drug-dependent patients. Enteral nutrition support with a polymeric formula should be attempted prior to PN when an oral diet is not tolerated.
2.2.7.2 Parenteral Nutrition:

Parenteral nutrition (PN) can provide nutrition to patients with active disease who meet one of the following criteria:

- Cannot tolerate adequate enteral feedings
- Obstruction and/or stricture present
- Distal fistula with inability to feed beyond site
- Severe short bowel syndrome (approximately less than 150 cm of small bowel remaining)

Use of PN has not been found to be effective as primary therapy in Crohn’s or UC. The use of preoperative PN has not been carefully studied in IBD and may be used for severely malnourished patients who meet the above criteria. Additional studies are needed to determine the precise role of perioperative PN in patients with IBD.

2.2.8 Nutrition as Supportive Therapy in Inflammatory Bowel Disease:

2.2.8.1 Short Chain Fatty Acids:

Short chain fatty acids (SCFAs) are by products of bacterial fermentation of undigested carbohydrates in the colon. In humans, acetate, butyrate and propionate are the predominant SCFAs providing up to 600 calories per day to the colonocyte (providing 70% of the energy needs to the colon). Factors that interfere in SCFA oxidation with active UC have been found to have a decreased colonic oxidation of butyrate that normalizes when remission is achieved. This has led to the study and development of SCFA enemas. Results using these enemas have shown some benefit in reducing colitis. SCFAs may also be effective in treating antibiotic induced diarrhea due to their participation in regulating water and electrolyte absorption in the colon.
2.2.8.2 Glutamine:

Glutamine has been studied in the treatment of IBD due to its role as a fuel for rapidly replicating cells such as those lining the intestinal tract mucosa. In animal studies, glutamine has been found to improve gut mucosa and decrease damage after certain drug treatments. There is no evidence to date that glutamine has a role in the therapy for IBD.

2.2.8.3 Omega 3 fatty acids:

Omega 3 fatty acids found in fish oil have been studied due to their anti-inflammatory properties. A decreased rate of relapse from remission has been shown in Crohn’s disease, although similar results have not been demonstrated in UC. This may be due in part to the poor tolerance of fish oil supplements leading to non-compliance. In addition, commercial varieties vary in their composition and may require several pills to achieve the desired dose used in studies to be effective. Side effects can include stomach upset.

2.2.8.4 Prebiotics & Probiotics:

The use of prebiotics and probiotics may prove to be beneficial in certain diseases, including IBD. Prebiotics are nondigestible food ingredients that can beneficially affect the host by selectively stimulating the growth and/or activity of a limited number of bacteria. Probiotics are viable microbial food ingredients that confer a benefit the health of the host.

2.2.8.4.1 Prebiotics:

Examples of prebiotics are fructooligosaccharides (FOS), inulin, lactulose and galactooligosaccharides. Food sources include onions, garlic, asparagus, leeks, bananas, artichokes and chicory root. Enteral tube feeding products containing FOS and inulin are now available (such as Peptamen with FOs/Inulin, Jevity Plus and Nepro). Prebiotics are water soluble, fermentable nonviscous fiber-like substances that exhibit a positive effect on intestinal transit in constipated patients. They act as fecal bulking agents due in part to their osmotic effect. Small amounts are recommended throughout the day due to this effect. Studies have shown that greater than 10 grams per day can cause increased diarrhea and cramping. Enteral tube feeding products on the market contain
approximately 4 to 8 grams per 1,000 calories. Studies have used anywhere between 3 and 20 grams per day. Prebiotics are currently used to treat encephalopathy: animal studies suggest a decreased risk of colon cancer.

**2.2.8.4.2 Probiotics:**

Probiotics are currently being studied at many institutions. The most widely used are Lactobacillus and Bifidobacterium. Probiotic use has been shown to decrease the temporary and duration of antibiotic associated diarrhea, rotavirus, C-difficile and traveler’s diarrhea. Eight randomized controlled trials have been completed with probiotics and IBD. Five of the trials, all involving Crohn’s or pouchitis cases, showed a significantly smaller percentage of relapses with probiotic therapy compared to the control group who received a placebo or 5ASA treatment. The three trials involving patients with UC found no significant difference in relapses, although two of the trials concluded probiotic therapy with E.coli Nissle 1917 was equivalent to 5ASA in maintaining remission.

Food products that are considered probiotics include fermented milk or pourable yogurt and yogurt with live cultures. Many commercial supplements, such as Lactinex, are available. Neither the FDA nor any federal agency routinely tests for quality of probiotics. Independent tests have revealed up to 30% of probiotics on the market lacked enough active bacteria. Products should reveal the “Live Active Cultures” seal with 108 viable lactic acid bacteria per gram or 107 for yogurt.

Although both Prebiotics and probiotics show much potential, more research in needed to determine efficacy, recommended use and dosing for the patient with IBD. One concern voiced against the uncontrolled use of Probiotics is that of creating “super bugs” in an era of multiple antibiotic resistant bacteria.

It is clear that nutrition plays an important role in the management of patients with IBD. Unfortunately, there is no clear nutrition “formulation” that works best for all patients. Attention to weight changes, eating habits, and GI symptoms are the best guides for the clinician. Thorough, ongoing nutrition assessment and a multidisciplinary approach are
keys to success. Table 9 provides a few useful websites for additional information on IBD and related topics.

2.2.9 New Endoscopic Approaches in IBD

Patients with long standing ulcerative colitis and Crohn’s disease are at an increased risk for the development of intraepithelial neoplasia (formerly known as dysplasia) and colorectal neoplasia. Therefore, surveillance endoscopy is mandatory in these patients. Nevertheless, standard white light endoscopy with multiple random biopsies may miss a quantum of lesions.

During the last ten years, a variety of new endoscopic techniques were introduced to improve diagnosis and patient outcome in inflammatory bowel disease (IBD). Traditionally, standard white light endoscopy only allows the investigation of the mucosal surface and surrounding blood vessels at low magnification.

**Figure No: 1**

**Endoscopy in IBD**

High-resolution standard white light endoscopic image of active Crohn’s disease. Endoscopy shows ulcerations, mucosal edema and erythema.

To overcome these limitations, new endoscopic imaging techniques were developed providing a more detailed view of the mucosa. Emerging endoscopic imaging techniques include chromoendoscopy and magnification endoscopy. Additionally, new endoscopic devices now allow real time in vivo histology during ongoing endoscopy.

This review describes the concept of advanced endoscopic techniques in IBD.

2.2.9.1 Chromoendoscopy:

Chromoendoscopy uses different staining techniques to enhance the mucosal detail and submucosal vascular pattern, thereby improving the detection of pathological lesions and enabling a more precise in dye-based and dye-less imaging techniques.

The basic principle of dye-based chromo endoscopy (DBC) is the use of biocompatible dye agents.

Figure No: 2

Dye-based chromoendoscopy-1
Dye-based chromoendoscopy

Chromo endoscopy with indigo carmine. A better distinction of Mucosal changes in long standing ulcerative colitis (A) and pit pattern analysis Of suspicious lesions (B).


Dyes include absorptive (methylene blue 0.1%-0.5%, cresyl violet 0.2%) and contrast agents (indigo carmine 0.2%-0.4%). DBC yields an additional diagnostic value with a 3-4 higher detection rate of intraepithelial neoplasia. However, dye based chromo endoscopy has some potential limitations. There are additional costs for the equipment needed for dye spraying, it is a time consuming procedure, the dye does not always coat the surface evenly and it does not allow for a detailed analysis of the sub epithelial capillary network, which is an important feature in the early diagnosis of gastrointestinal neoplasia.

Therefore, dye-less chromo endoscopy (DLC; also called virtual chromo endoscopy) has been developed.
Figure No: 4

Dye-less Chromoendoscopy-1

Figure No: 5

Dye-less Chromoendoscopy-2
Figure No: 6

Dye-less Chromoendoscopy-3

Figure No: 7

Dye-less Chromoendoscopy-4

Virtual chromoendoscopy using the fujinon intelligent color Enhancement-system. A: Shows standard white light endoscopic image; B-D: Illustrate different fujinon intelligent color enhancement settings to improve mucosal Detail.


DLC includes narrow band imaging (NBI; Olympus, Tokyo, Japan) and i-Scan (Pentax, Tokyo, Japan).
NBI is based on optical filters within the light source of the endoscope which narrow the bandwidth of spectral transmittance such that the blood vessels are enhanced and thus seen more easily.

FICE and i-Scan are based on the same physical principle as NBI, but due to a computed spectral estimation technology, they are not dependent on the presence of optical filters inside of the video endoscope. In contrast to NBI, FICE and i-Scan use an endoscopic image from the video processor and reconstruct virtual images in real time by increasing the intensity of narrowed blue light to a maximum and by decreasing narrowed red light and green light to a minimum resulting in an improved contrast of the capillary patterns and enhancement of the mucosal surface.

One recent study evaluated magnifying colonoscopy with NBI for the diagnosis of intraepithelial neoplasia in ulcerative colitis. It was found that the tortuous pattern determined by NBI colonoscopy may be a clue for the identification of dysplasia during surveillance for ulcerative colitis. Another study included 50 patients with longstanding ulcerative colitis and reported on a moderate accuracy (sensitivity 75%, specificity 81%) for the NBI diagnosis of intraepithelial neoplasia. Additionally, NBI colonoscopy may be of value for determining the grade of inflammation in patients with quiescent ulcerative colitis.

Very recently, it was shown the FICE could not improve the detection or delineation of ulcers and erosions due to Crohn’s disease. Nevertheless, these preliminary data have to be proven in larger prospective trials.

One recent published study tested the efficacy of high definition endoscopy alone compared to i-Scan or chromo endoscopy with methylene blue (0.1%) in screening for colorectal cancer. It was found that both i-Scan and chromo endoscopy identified more lesions compared to high definition endoscopy alone. Additionally, i-Scan was able to predict neoplasia as precisely as chromo endoscopy.
2.2.9.2 Magnification Endoscopy:

Magnification endoscopy (also called zoom endoscopy) utilizes a movable lens to vary the degree of magnification up to 150-fold.

Figure No: 8

Magnification Endoscopy

By staining the entire colon with methylene blue, it has been shown that chromoendoscopy combined with magnification endoscopy has the potential to improve targeting biopsy examination in patients with long-standing colitis and facilitate early detection of intraepithelial neoplasia and colorectal cancer. In the chromo endoscopy arm a significantly better correlation was found between the endoscopic assessment of degree (p = 0.0002) and extent (p < 0.0001) of colonic inflammation and the histopathologic findings compared with the conventional colonoscopy group. Additionally, more targeted biopsies were possible, and significantly more intraepithelial neoplasia were detected in the chromo endoscopy group (p = 0.003).

Hurlstone DP et al. (2004) were confirmed this data in a prospective study, 162 patients with long standing ulcerative colitis underwent total colonoscopy. After detection of
subtle mucosal changes intravital staining with indigo carmine was used. Subsequently, the macroscopic type and the staining pattern were defined. Chromo endoscopy with magnification and targeted biopsies significantly increased diagnostic yield for intraepithelial neoplasia and the number of flat neoplastic changes as opposed to conventional colonoscopy.

The largest prospective study to date comparing conventional endoscopy with magnification endoscopy enrolled 300 patients with ulcerative colitis. Magnification imaging was significantly better than conventional colonoscopy for predicting disease extent in vivo (p < 0.0001). The authors concluded that high-magnification imaging provides a sensitive and specific in vivo “virtual biopsy” in ulcerative colitis. High-accuracy optical biopsy could limit the number of biopsies required, with significant cost savings for pathology services.

2.2.9.3 Spectroscopy:

Spectroscopy includes several includes optical techniques, including fluorescence, reflectance, light scattering spectroscopy and optical coherence tomography. Spectroscopy depends on the wavelength of the light source and on tissue characteristics. Based on differences between the spectra of light that is backscattered between cells, different spectra can be identified that are specific for various diseases such as ischemia, inflammation, and malignancy.

One study assessed fluorescence endoscopy for the detection of intraepithelial neoplasia in ulcerative colitis by taking optical guided biopsies. By using 5-aminolevulinic acid as an exogenous fluorophore agent, sensitivity and specificity for dysplastic lesions was 100% and 62%, respectively. Very recently, the detection of invisible flat intraepithelial neoplasia with protoporphyrin IX fluorescence was compared to standard 4-quadrant biopsies. Flat intraepithelial neoplasia was detected in 7% of patients by standard white light 4-quadrant biopsies and in 24% of patients using fluorescence-guided endoscopy (p = 0.02). Sensitivity and specificity for differentiating patients with and without dysplasia were 100% and 81%, respectively. Additionally, dysplastic and non-dysplastic mucosa could be discriminated with a sensitivity and specificity of 73% and 81%, respectively.
2.2.9.4 Confocal Laser Endomicroscopy:

In 2004, Confocal laser Endomicroscopy was introduced, allowing real time in vivo histology of 1000-fold magnification during ongoing endoscopy. Currently, two FDA approved devices are available.

**Figure No: 9**

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy using either the integrated system (iCLE, A) or the probe-based system (pCLE, B) visualizes dilated microvessels, leakage and disturbed crypt architecture in active ulcerative colitis.


One is integrated into the distal tip of a high resolution endoscope (iCLE; Pentax, Tokyo, Japan), one represents a stand-alone probe which is capable of passage through the working channel of most standard endoscopes (pCLE; Cellvizio, Mauna Kea Technologies, Paris, France). A blue laser light source delivers an excitation wavelength of 488 nm and returning light is detected at > 505 nm. Endomicroscopy requires the application of fluorescence agents, either systemically (fluorescein) or topically (e.g. acriflavine, cresyl violet).
While endomicroscopy only covers a limited field of view within the mucosa, panoramic endomicroscopy of the whole gastrointestinal tract is not feasible. Therefore, macroscopic visualization of suspected areas is necessary before performing targeted endomicroscopy.

To date, different studies have addressed the utility of endomicroscopy for the in vivo diagnosis of IBD associated mucosal changes.

To compare endomicroscopic imaging of inflamed and non-inflamed rectal mucosa in patients with ulcerative colitis, Watanabe et al enrolled 17 patients with ulcerative colitis and 14 controls. Confocal images were compared to standard histopathology. Endomicroscopy was able to visualize crypt architecture, capillaries and inflammatory cells, providing equivalent information to histopathology.

Recently, a new classification of inflammation activity in ulcerative colitis using endomicroscopy for the in vivo evaluation of Crohn’s disease associated changes. Using the pCLE system, endomicroscopy was able to diagnose Crohn’s disease associated changes with high accuracy. Furthermore, pCLE could detect residual macroscopic non-visible mucosal inflammation as precisely as histology (k Values, 1.8, unpublished data).

Current guidelines recommend a large number of biopsy specimens during surveillance colonoscopy in ulcerative colitis. Nevertheless, flat lesions still may be missed. In a trial of longstanding ulcerative colitis, chromo endoscopy was used to unmask lesions for endomicroscopy and compared with standard white light endoscopy with random biopsies. Chromo endoscopy in combination with endomicroscopy detected 4.75 fold more neoplasia compared to conventional colonoscopy (p = 0.005). Additionally, 50% fewer biopsy specimens were required (p = 0.008). The presence of neoplastic changes could be predicted with high sensitivity, specificity and accuracy (94.7%, 98.3%, and 97.8%, respectively).

One recent study prospectively evaluated the clinical applicability and predictive power of endomicroscopy for the in vivo differentiation of dysplasia-associated lessional mass (DALM) or adenoma-like mass (ALM). Accuracy of endomicroscopy was 97% and an
excellent agreement between endomicroscopy and histopathological diagnosis was found (k = 0.91).

2.2.9.5 Endocytoscopy:

Endocytoscopy (Olympus, Tokyo, Japan) is a new imaging technique, enabling microscopic imaging of the mucosal layer of the gut at a magnification up to 1400-fold.

Figure No: 10

Endocytoscopy enables visualization of different cytological and architectural features, including size, arrangement, and density of cells.


Endocytoscopy is based on a contact light microscope which enables real-time visualization of cellular structures of the superficial-epithelial layer in a plane parallel to the mucosal surface. Currently, systems integrated into the distal tip of an endoscope (iEC) and probe-based (pEC) systems are available. Probe-based systems consist of handheld miniprobes, which are capable being inserted through the accessory channel of a standard endoscope. The device provides ultra high magnification imaging at × 570 (pEC), × 580 (iEC) or × 1400 (pEC) on a 19-inch monitor from an optical sampling site of about 0.5 mm in diameter. Endocytoscopy requires preparation of the mucosal layer with absorptive contrast agents like methylene blue or toluidine blue.
Recently, Endocytoscopy has been established as a useful tool to examine mucosal surfaces. Different studies suggest the potential of Endocytoscopy for the in vivo evaluation of duodenal mucosa in celiac disease. Furthermore, Endocytoscopy was able to detect tissue abnormalities in normal mucosa surrounding colorectal cancer and to identify neoplasia in aberrant crypt foci. Additionally, Endocytoscopy was shown to distinguish neoplastic from non-neoplastic lesions, and also to differentiate invasive colon cancer from adenoma.

Currently, data on Endocytoscopy for in vivo diagnosis of IBD are still lacking. Nevertheless, this new imaging technique is a promising development allowing surface magnification at cellular and sub cellular resolution.

2.2.9.6 Capsule Endoscopy:

In order to evaluate the small intestine capsule endoscopy (CE) was introduced. Currently two CE systems are available. One is distributed by Given Imaging (Norcross, Ga), and one by Olympus (Tokyo, Japan). The capsule is passively propelled through the intestine by peristalsis while transmitting color images of the intestine.

CE is useful for the evaluation of the small intestine in patients in whom the diagnosis of Crohn’s disease is elusive. Due to the danger of capsule retention in patients with established Crohn’s disease, a patency capsule is available which is self-dissolved approximately 30 h after ingestion. In addition, balloon-guided endoscopy could be used to remove impacted capsules. Dubcenco and coworkers studied CE findings in patients with established and suspected small-intestine Crohn’s disease and correlated the findings with radiologic, endoscopic and histologic findings. Final diagnosis of active small-intestine Crohn’s disease was made in 74% of patients. In addition, CE yielded a sensitivity and specificity of 89.6% and 100%, respectively, and a positive predictive value and a negative predictive value of 100% and 76.9%, respectively. Furthermore, CE was shown to be superior compared to push enteroscopy and enteroclysis.
2.3 Conclusion:

Neumann H. (2011) in Modern endoscopy has revolutionized the diagnosis and management of patients with IBD. The newly developed endoscopic devices offer features that allow more and more mucosal and sub mucosal details to be seen. According to high magnification and respective reduced field of view, prior assessment of suspicious lesions is mandatory. Chromo endoscopy, using either vital or virtual staining techniques unmasks circumscript lesions and confocal laser endomicroscopy or Endocytoscopy can then be used to predict intraepithelial neoplasia with high accuracy. Nevertheless, the assessment of these new endoscopic imaging modalities in clinical practice still warrants further investigation. In addition, currently there is no reimbursement for advanced endoscopic imaging methods including endomicroscopy, Endocytoscopy and spectroscopy. Therefore, endoscopy with multiple random biopsies remains the gold standard for surveillance in patients with IBD.

2.4 Role of Dietitian for the Treatment of Ulcerative Colitis:

Herbold N. H. et al and Mahan K. et al suggested that there is currently no established dietary treatment for ulcerative colitis. In general patients are recommended to follow healthy eating advice. Some people may find symptom relief from a low-fiber and or low-lactose diet at time of active disease. Support form a dietitian is important to ensure a nutritionally adequate diet is maintained if such dietary exclusions are made. As with crohn’s disease, nutritional support has a valuable role in this group of patients.

The following list will assist the dietitian in answering food tolerance questions for patients for either Crohn’s Disease (most often affecting the small intestine) or ulcerative colitis (affecting only the large intestine). As well as this list will be useful to the patients for getting their answers related to food tolerance questions for either of both the diseases. Some of the side effects of IBD may include deficiencies. There is no specific diet for either Crohn’s or ulcerative colitis, except to try to provide a well-balanced diet to assure adequate calories, vitamins, and minerals. Certain foods (listed as follows) may/may not have an impact on relieving the symptoms; however, individuals may have their own intolerances and would need to avoid/restrict those foods.
<table>
<thead>
<tr>
<th><strong>Problem</strong></th>
<th><strong>Do’s and Don’ts</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea- Do’s:</strong></td>
<td><strong>Don’ts:</strong></td>
</tr>
<tr>
<td>Severe diarrhea can cause malabsorption of nutrients, loss of electrolytes (especially sodium and potassium), minerals, and trace elements (especially zinc and magnesium). A trial with a clear liquids diet including fat-free broth, fruit ice, tea and clear juices can usually be introduced. Oral glucose electrolyte solutions with added potassium can help to replace electrolytes and fluids. Physician management with intravenous hydration and electrolyte replacements may also be necessary depending on the severity of the diarrhea and the patient’s ability to take in sufficient oral fluids. To control diarrhea and malabsorption of nutrients, a low-fat, low-fiber diet may be followed initially, such as white bread, cereals with fiber less than 3 gms, rice, potato, green beans, carrots, and canned peaches. Applesauce, which contains pectins, may also help the diarrhea. Low fiber helps to minimize the irritation to the inflamed bowel, slow the intestinal transit rate, and reduce stool frequency. Low fat may control the symptoms of steatorrhea (fat malabsorption). Gradually advance the diet as tolerated to also include protein foods, such as lean chicken, fish, pork, and beef.</td>
<td>Don’t serve high-fiber foods, such as whole-grain breads, cereals, skins from fresh fruits and vegetables, nuts and seeds. The amount of fiber tolerated varies between patients and usually can be increased when diarrhea subsides. Don’t serve a prolonged low-fiber diet. Don’t serve large amounts of sucrose, found in table sugar, maple syrup, fruit, vegetables, honey, and in certain desserts and beverages. Don’t consume large amounts of resistant (more, difficult to digest) starches, particularly found in legumes, cooked and cooled potatoes, rice and pasta, and under-ripe bananas. Don’t ignore the effect of lactose in some patients. Some patients may require limiting lactose from dairy products. (In patients with Crohn’s disease, lactose is absorbed in the small intestine). However, oftentimes limiting lactose is based on individual tolerance level. Don’t serve caffeinated and alcoholic beverages (particularly beer and wine) because they increase GI secretions and colonic motility. Don’t forget to consult with the physician or dietitian before taking the vitamin</td>
</tr>
</tbody>
</table>
Total elimination of lactose products is not always necessary. Try lactase-tested milk or lactase pills if a dairy product causes GI upset.

Require vitamin/mineral supplement given the severity of the diarrhea and/or vitamin and mineral losses.

In Crohn’s disease, resection of the distal small bowel can result in bile salt deficiency and subsequent fat malabsorption and fat-soluble vitamin (vitamin A, D, E, K) deficiency, therefore requiring vitamin repletion. If the ileum is resected, vitamin B12 deficiency can develop. Repletion with vitamin B12 injections is one option.

<table>
<thead>
<tr>
<th>Nausea- Do’s:</th>
<th>Don’ts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depending on the severity of the nausea, provide a concomitant treatment with antiemetic therapy and a clear liquid diet (broth, fruit ice, black tea, gelatin), followed by toast (dry or with jelly) and crackers (saltines). If the patient continues to tolerate the diet, slowly resume low-fat, low-fiber diet. Have the patient drink fluids between meals rather than with meals.</td>
<td>Don’t serve high-fat. Greasy meals. Don’t serve large, high-fat meals. Don’t forget to avoid food odors by eating cold food or food at room temperature. Don’t allow the patient to eat 1 to 2 hours before lying down.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdominal Pain- Do’s:</th>
<th>Don’ts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue with low-fat, low-fiber diet, but also incorporate small frequent feedings (eating approximately every 2-3 hours</td>
<td>Don’t serve large, high-fat meals</td>
</tr>
</tbody>
</table>
during the day).

<table>
<thead>
<tr>
<th>Weight loss- Do’s:</th>
<th>Don’ts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small frequent feedings with nutrient-dense foods should be included in diet.</td>
<td>Don’t consume large amounts of fruits, nonstarchy vegetables, and salads because these items are too low in calories.</td>
</tr>
<tr>
<td>Snacks, such as peanut butter, cheddar cheese on crackers, low-fat yogurt, and puddings, as tolerated may be offered.</td>
<td>Don’t consume large quantities of sugar-free/calorie-free beverages.</td>
</tr>
<tr>
<td>Consider a high calorie/protein liquid oral supplement between meals. If the patient can tolerate ice cream, try adding in to the supplement for additional calories and protein.</td>
<td></td>
</tr>
</tbody>
</table>

2.5 Abstract of Research.

Nazario B (2011) describes that how ulcerative colitis diet can help to manage the treatment of it. How does it affect to it. It’s important to self manage ulcerative colitis with healthy life style habits and a nutrient-rich diet. Paying attention to the nutrition is especially important with GI diseases because the symptoms of diarrhea and bleeding can lead to dehydration, electrolyte imbalance, and loss of essential nutrients. That can lead to a host of problems such as fatigue, weakness, and anemia.

Dr. Saibil Fred (2003) Explains about the Alternative treatments, homeopathy, Ayurveda and naturopathy. About 25% of inflammatory bowel disease patients use alternative treatments. Many of them are ulcerative colitis sufferers. Unconventional therapies and alternative approaches might help to make you symptom free. This is considered as complementary therapy. Today an alternative treatment or therapy is included by many ulcerative colitis sufferers as one of their standard treatment options. These include unorthodox treatments (Homeopathy, Ayurveda etc.), dietary modification, antioxidants, herbals, bacterial re-colonization, fats and oils, yoga etc.
Homeopathy is useful in the treatment of ulcerative colitis especially in the early stages of the disease condition. Homeopathic remedies are prescribed basically by symptoms and then by condition. Homeopathic doctors claim that it treats ulcerative colitis at roots. They can slow down the progress of the disease that could help you to avoid surgery. Some patients find them helpful.

Ayurveda literally means ‘the science of life’. This is a natural healing system developed by India. Ayurveda is considered a safe medicine without any side effects as it is made from natural products. Ayurveda medicine is not refined like unconventional medicine. The following Ayurveda medicine has helped me a lot at some points

Naturopathic treatments for ulcerative colitis are also available. It is considered that in this approach body will do the healing work automatically and naturally by applying an individual treatment plan depending on symptoms of the patient.

SEROVERA is a complete GI specific program that has probiotics and healing benefits from Aloe Vera. SEROVERA AMP500 contains the full-spectrum of healing agents as their company illustrated. This is a combined therapy that includes probiotics and Aloe Vera. Aloe is known to be an anti-inflammatory
Aloe Mucilaginous Polysaccharides (AMP) is considered as an effective supplement you can use to fight digestive disorders including ulcerative colitis disease and Crohn’s disease. AloeElite for one is safe and all natural made of Certified Organically Grown plants.

- Natural remedies to reduce inflammation like omega 3 fatty acids may reduce inflammation in people with ulcerative colitis. Whereas, Folic acid reduces the risk of colon cancer in Ulcerative colitis patients. Also, Turmeric is a powerful anti-oxidant and it prevents cell aging. Turmeric supports the body’s natural anti-inflammatory response that promotes joint health. Bromelain is a mixture of protein-digesting enzymes derived from pineapple stem that is believed to reduce inflammation. A Duke University study on animals found it beneficial to decrease the incident and severity of colitis. As well as Acupuncture helps to relieve pain from blocked energy along energy pathway in the body. It could helpful for some patients to control ulcerative colitis.

- Steinhart Dr. Hillary A. (2011) reported that many people think yoga, meditation, biofeedback etc. can play an important role in helping you be symptom free. Do regular exercise to stimulate your body and to increase your cardiovascular system. Walking is good.

- Prasad Raman (2003) reports Diet is a very important aspect of keeping your ulcerative colitis under control, because food directly affects the bacterial ecology of the gut. Nutritionists say carbohydrates may be a food for potentially harmful bacteria and harmful bacteria balance could be restored. The most popular diet for ulcerative colitis patients is known as Specific Carbohydrate Diet (SCD). There are some other diets that Ulcerative Colitis patients are following: low residue diet, gluten free diet, lactose free diet, raw food diet, low fiber diet etc.

2.5.1 Studies on L-Glutamine:

- Fresenius Kabi (2011) has justified about their Product Kabimmune about its beneficial properties that L-glutamine is one of the most important nutrients for your intestines. L-glutamine is the primary energy source for your immune
system. It has the ability to “repair leaky gut syndrome” by maintaining the integrity of the bowels.

**Figure No: 12**

![Kabimmune](image)

Photo courtesy: [www.freseniuskabi.com](http://www.freseniuskabi.com)

They have suggested that if you are suffering from diarrhea, mix 1 teaspoon of L-glutamine powder in a little water, and drink it on an empty stomach, and that should stop your diarrhea pretty quickly. But, the reason to take L-glutamine on a daily and continued basis is for: colonic repair. There is no daily requirement for glutamine because the body can make its own supply. As mentioned earlier, various severe stresses may result in a temporary glutamine deficiency. High-protein foods such as meat, fish, beans and dairy products are excellent sources of glutamine. Typical daily intake from food ranges from approximately 1 to 6 g. typical therapeutic dosages of glutamine used in studies range from 3 to 30 g daily, divided into several separate doses.

Khogali SE et al (2002) noted that Angina is too dangerous a disease for self-treatment. If you have angina, do not take glutamine (or any other supplement) except on the advice of a physician. Because, as noted above, cells of the intestine use glutamine for fuel, the supplement has been tried as a supportive treatment for various digestive conditions, with mixed results. They have also studied and conducted investigations in rats and found that glutamine could protect the heart from damage caused by loss of oxygen. Based on these findings, they went on to evaluate the effects of glutamine in ten people with chronic angina who were also taking standard medication. In this double-blind, placebo-
controlled trial, each participant received a single oral dose of glutamine (80 mg per kg of body weight) or placebo 40 minutes before a treadmill test. A week later, each participant received the opposite treatment. The results showed that use of glutamine significantly enhanced the ability of participants to exercise without showing signs of heart stress. Based on the results in rats, researchers suggest that a higher dose of glutamine would be worth trying.

Huffman FG (2003) tested uses include reducing diarrhea caused by the drug nelfinavir (used for treatment of HIV). They have also studied one double-blind, placebo-controlled study of 25 people found that use of glutamine at 30 g daily for 7 days reduced diarrhea caused by the protease inhibitor nelfinavir. They also reported Nelfinavir or other protease inhibitors for HIV, or cancer chemotherapy drugs: Use of glutamine may reduce intestinal side effects.

Candow DG and Antonio J (2001) reported glutamine has been tried as an ergogenic aid for body builders, but two small trials failed to find any evidence of benefit. Based on glutamine’s role in muscle, it has been suggested that glutamine might be useful for athletes experiencing overtraining syndrome. As the name suggests, this syndrome is the cumulative effect of a training regimen that allows too little rest and recovery between workouts. Symptoms include depression, fatigue, reduced performance, and physiological signs of stress. Glutamine supplements have additionally been proposed as treatment for attention deficit disorder, ulcers, and as a “brain booster”. However, there is little to no scientific evidence for any of these uses. They have reported a double-blind; placebo-controlled trial of 31 people ranging from 18 to 24 years of age evaluated the potential benefits of glutamine as a sports supplement for improving response to resistance training (weight lifting). Participants received either placebo or glutamine at a dose of 0.9 g per kg of lean tissue mass. After 6 weeks of resistance training, participants taking glutamine showed no relative improvement in performance, composition or muscle protein degradation.

Clark RH (2000) studied another small double-blind trial found that combination treatment with glutamine, arginine, and beta-hydroxy beta-methyl butyrate (HMB) could increase muscle-mass and possibly improve immune status.
Deniele B (2001) reported that there is mixed evidence regarding whether glutamine can reduce the side effects of cancer chemotherapy. A double-blind, placebo-controlled trial of 70 people undergoing chemotherapy with the drug 5-FU for colorectal cancer found that glutamine at a dose of 18 g daily improved intestinal function and structure, and reduced the need for anti-diarrheal drugs.

Amara S (2008) studied, based on a review of several studies, there is some preliminary evidence that glutamine may help relieve the pain associated with nerve damage (peripheral neuropathy) caused by some chemotherapy drugs.

Antonio J et al (2002) also reported that similarly the negative results were seen in a small double-blind, placebo-controlled trial of weightlifters using a dose of 0.3 g per kg of total body weight.

Shao A and Hathcock JN (2008) reported L-glutamine is a naturally occurring amino acid, glutamine is thought to be a safe supplement when taken at recommended dosages. There is strong evidence that glutamine is safe at levels up to 14 g per day, although higher dosages have been tested without apparent adverse effects. Nevertheless, those who are hypersensitive to monosodium glutamate (MSG) should use glutamine with caution, as the body metabolizes glutamine into glutamate. Also, because many anti-epilepsy drugs work by blocking glutamate stimulation in the brain, high dosages of glutamine might conceivably overwhelm these drugs and pose a risk to people with epilepsy. In one case report, high doses of the supplement L-glutamine (more than 2 g per day) may have triggered episodes of mania in two people not previously known to have bipolar disorder.

Galera SC (2010) also reported that in a small randomized trial including 30 older people, L-glutamine did not cause any clinically significant changes in lab tests. The researchers did urge caution, though, since there were some statistically significant changes for certain kidney levels. Maximum safe dosages for young children, pregnant or nursing women, or those with severe liver or kidney disease have not been determined.

- Interactions of some of the medications with the L-glutamine one should know about:
• Antiseizure medications, including carbamazepine, Phenobarbital, phenytoin (Dilantin), primidone (Mysoline), and valproic acid (Depakene): Use glutamine under medical supervision.

• Huffman FG 2003 Reported Nelfinavir or other protease inhibitors for HIV, or cancer chemotherapy drugs: Use of glutamine may reduce intestinal side effects.

2.5.2 Studies on Omega 3 fatty Acid:

Figure No: 13

Simpoulos AP (2002) reported that the diet of our ancestors was less dense in calories, being higher in fiber, rich in fruits, vegetables, lean meat, and fish. As a result, the diet was lower in total fat and saturated fat, but contained equal amounts of n-6 and n-3 essential fatty acids. Linoleic acid (LA) is the major n-6 fatty acid, and alpha linolenic acid (ALA) is the major n-3 fatty acid. In the body, LA metabolized to Arachidonic acid (AA), and ALA is metabolized to eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). The ratio of n-6 to n-3 essential fatty acids was 1 to 2:1 with higher levels of the longer-chain polyunsaturated fatty acids (PUFA), such as EPA, DHA and AA, than today’s diet. Today this ratio is about 10 to 1:20 to 25 to 1, indicating that western diets are deficient in n-3 fatty acids compared with the diet on which humans evolved and their genetic patterns were established. The n-3 and n-6 EPA are not interconvertible in the human body and are important components of practically all cell membranes. The n-6
and n-3 fatty acids influence eicosanoid metabolism, gene expression, and intracellular cell to cell communication. The PUFA composition of cell membranes is, to a great extent, dependent on dietary intake. Therefore, appropriate amounts of dietary n-6 and n-3 fatty acids need to be considered in making dietary recommendations. These two classes of PUFA should be distinguished because they are metabolically and functionally distinct and have opposing physiological functions; their balance is important for homeostasis and normal development. Studies with nonhuman primates and human newborns indicate that DHA is essential for the normal functional development of the retina and brain, particularly in premature infants. A balanced n-6/n-3 ratio in the diet is essential for normal growth and development and should lead to decreases in cardiovascular disease and other chronic diseases and improve mental health. Although a recommended dietary allowance for essential fatty acids does not exist, an adequate intake (AI) has been estimated for n-6 and n-3 essential fatty acids by an international scientific working group. For western societies, it will be necessary to decrease the intake of n-6 fatty acids and increase the intake of n-3 fatty acids. The food industry is already taking steps to return n-3 essential fatty acids to the food supply by enriching various foods with n-3 fatty acids. To obtain the recommended AI, it will be necessary to consider the issues involved in enriching the food supply with n-3 PUFA in terms of dosage, safety, and sources of n-3 fatty acids.

Belluzzi A. et al. (2002) studied that the clinical studies of the use of polyunsaturated long-chain fatty acids in the treatment of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn’s diseases. The reasons for the discrepancies in the findings could be related to the different study designs, different treatments, overlapping of treatment effects, as well as the variety of treatment formulations and doses used, which have led to results that are, in certain instances, very difficult to explain. Emphasis on a treatment formulation which reduces the incidence of side effects, together with careful selection of patients and experimental design, seems to be associated with benefits, and these studies point to the therapeutic potential for these lipids in the therapy of IBD. It is possible that these fatty acids act by reducing low-grade active inflammation rather than by preventing reinitiation of the inflammatory process from a truly quiescent state. Whether this treatment is applicable to all IBD patients has not been fully elucidated.
Nevertheless, taken together, all these studies suggest the effectiveness of these new therapeutic approaches, not only when conventional treatment fails or when it is not possible to treat chronically, but also, in some instances, as first choice.

Campos F.G. et al. (2002) reported the effects of parenteral lipid emulsions (LE) enriched with n-3 fatty acids (n-3 FA) in experimental acute colitis. Seventy-four adult male Wistar rats were randomized into six groups, five of which had acetic acid-induced colitis. The animals received a fat-free diet and water ad libitum in individual metabolic cages. By a central venous catheter, saline was infused (0.5 ml/h) into the control groups CS (without colitis) and CC (with colitis), while the test groups received specific LE for 7 days. The n-3/n-6 FA ratio and the lipidic compositions regarding long chain (LCT) and medium chain (MCT) triglycerides were: group L-1:7:7 (LCT n = 12), M-1:7:0 (MCT and LCT, n = 12), LW-3-1:4.5 (LCT plus n-3 FA, n = 12) and MW-3-1:3.0 (MCT and LCT plus n-3 FA, n = 13). The frequency of diarrhea, oral intake/body weight ratio, intestinal alterations, macrophage cellularity were evaluated and colonic concentrations of leukotrienes (LTB4, LTC4), prostaglandins (PGE2) and thromboxanes (TXB2) were measured. Groups M, MW-3 and LW-3 had less diarrhea than the CC group (p<0.05). Average oral intake/body weight ratio in MW-3 animals was comparable to the CS and better than the CC group. N-3 FA treated rats (LW-3 and MW-3) presented less intestinal inflammatory alterations than CC rats. Mucosal ulcer formation in MW-3 group did not differ from CS rats. M and MW-3 rats had less macrophage in the colon than the CC group. Compared with CC group, lower concentrations of LTB4 in the CS, LW-3 and MW-3 groups; of PGE2 in the CS, M and MW-3 groups; and of TXB2 in the CS and MW-3 groups were found. Mean concentrations of LTC4 did not differ among the groups. Thus, a LCT-containing LE with a low n-3-n-6 ratio does not modify inflammatory colitis manifestations; LE with a high n-3-n-6 ratio reduces diarrhea. Preserves oral intake-weight ratio, attenuates morphological consequences and decrease colonic concentrations of inflammatory mediators; MCT/LCT- containing LE with 1:3 n-3-n-6 ratio exerts the most profound beneficial impact on the inflammatory response.

Belluzzi A. (2004) studied there is considerable evidence to suggest that polyunsaturated fatty acids (PUFAs) alleviate a number of inflammatory diseases, mainly the fish derivatives, n-3 PUFAs. Researchers aim is to briefly review the literature involving
clinical interventions with these lipid compounds in the treatment of Ulcerative Colitis (UC) and Crohn’s Disease (CD), Inflammatory Bowel Disease (IBD). Data available are conflicting and the reason for the discrepancies in the findings could reside in the different study designs. Often studies are limited by the choice of placebo and insufficient washout period and direct comparison of trials is hampered by the use of various formulations and dosages of n-3 PUFAs.

The importance of the n-3 PUFAs formulation in lowering the incidence of side effects along with careful selection of patients and experimental design seems to be associated with benefits. It is possible these fatty acids act by reducing low-grade active inflammation rather than by preventing reinitiation of the inflammatory process from a truly quiescent state. Whether this treatment is applicable to all patients with IBD has not been fully elucidated. Nevertheless, taken together, all these studies suggest the effectiveness of these new therapeutic approaches, not only when the conventional treatment fails or it is not possible to treat chronically, but also, in some instances as first choice.

Calder P. (2009) also studied fatty acids may influence immune function through a variety of mechanisms; many of these are associated with changes in fatty acid composition of immune cell membranes. Eicosanoids produced from Arachidonic acid have roles in inflammation and immunity. Increased membrane content of n-3 fatty acids results in a changed pattern of production of eicosanoids, resolvins, and cytokines. Changing the fatty acid composition of immune cells also affects T cell reactivity and antigen presentation. Little attention has been paid to the influence of fatty acids on the gut associated lymphoid tissue. However, there has been considerable interest in fatty acids and gut inflammation.

Cabre E, Manosa M & Gassull M. (2012) reported despite their well known anti-inflammatory actions, the clinical usefulness of omega-3 PUFA in inflammatory bowel disease is controversial. Researcher aimed to systematically review the available data on the performance of omega-3 PUFA as therapeutic agents in these patients. Electronic databases were systematically searched for RCT of fish oil or omega-3 PUFA therapy in both active and inactive ulcerative colitis of Crohn’s disease, without limitation on either
the length of therapy or the form it was given, including nutritional supplements and enteral formula diets. Eligible articles were assessed for methodological quality on the basis of the adequacy of the randomization process, concealment of allocation, blinding of intervention and outcome, possible biases, and completeness of follow-up. The five-point Oxford quality score was calculated. A total of 19 RCT were finally selected for this review. Overall, available data do not allow to support the use of omega-3 PUFA supplementation for the treatment of both active and inactive inflammatory bowel disease. Negative results are quite consistent in trials assessing the use of omega-3 PUFA to maintain disease remission, particularly ulcerative colitis, and to a lesser extent Crohn’s disease. Trials on their use in active disease do not allow to draw firm conclusions mainly because the heterogeneity of design (ulcerative colitis) or their short number (Crohn’s disease). In most trials, the appropriateness of the selected placebo is questionable. The present systematic review does not allow making firm recommendations about the usefulness of omega-3 in inflammatory bowel disease.

Figure No: 14

Photo courtesy: www.walgreens.com, Date: 25/09/2013, Time: 1:30 pm

Innis S. and Jacobson K. (2007) studied that inflammatory bowel disease are life-long reoccurring inflammatory disorders of the gastrointestinal tract and have been increasing in incidence in recent decades, notably in the pediatric population. Although genetic predisposition remains an important factor, this increased incidence most likely reflects an environmental change. One potential contributor to this is the change in dietary fat intake, with dietary intake of n-6 polyunsaturated fatty acids (PUFAs) following a similar
temporal pattern to the change in inflammatory bowel disease incidence. Dietary n-6 PUFAs comprise a major, modifiable, environmental factor known to promote a heightened inflammatory response through a number of pathways, including their role as precursors for synthesis of eicosanoids and their inhibitory effect on the synthesis of the n-3 PUFAs eicosapentanoic acid and do-cosahexanoic acid. The increase in n-6 PUFA intake affects individual of all ages, with fetal PUFA accretion and infant dietary PUFA intake from breast milk reflecting maternal dietary intake. A high level of n-6 PUFA in milk results in increased n-6 PUFA in colonic phospholipids and an exaggerated inflammatory response to chemically induced colitis. Conversely, during development, a diet low in n-6 PUFAs and high in n-3 PUFAs increases colonic n-3 fatty acids, attenuates the inflammatory response, and lowers colonic damage. High dietary n-6 PUFA intake may be an important environmental modifier that contributes to inflammatory bowel diseases.

Rajendran N. and Kumar D. (2010) reported many studies have looked at connections between diet, etiology, signs and symptoms associated with inflammatory bowel disease (IBD). Although these connections are apparent to clinicians, they are difficult to prove qualitatively or quantitatively. Enteral feeding and polymeric diets are equally effective at bringing about remission in Crohn’s disease (CD). Parenteral feeding is also effective, although none of these methods is as effective as corticosteroid therapy. However, enteral feeding is preferred in the pediatric population because linear growth is more adequately maintained via this route. Exclusion diets in patients brought into remission using an elemental diet have been shown to maintain remission for longer periods. Studies that aim to isolate culpable food groups have shown that individuals react differently on exposure to or exclusion of various foods. The commonly identified food sensitivities are cereals, milk, eggs, vegetables and citrus fruits. Studies that have looked at gut mucosal antigen behavior have shown higher rectal blood flow, in response to specific food antigens, in those with CD over healthy subjects. Exclusion of sugar shows little evidence of amelioration in CD. Omega 3 fatty acids show promise in the treatment of IBD but await larger randomized controlled trials. Patients frequently notice that specific foods, with advances in the laboratory tests and food supplements available, the aim is to
prolong remission in these patients using dietary measures, and reduce the need for pharmacotherapy and surgical intervention.

Turner D, Steinhart AH, Griffiths AM. (2007) reported that omega-3 fatty acids (n-3, fish oil) have been shown to anti-inflammatory properties. Therefore, n-3 therapy may be beneficial in chronic inflammatory disorders such as ulcerative colitis. The three studies that were included used different formulation and dosing of n-3 but none used enteric coated capsules. The pooled analysis showed a similar relapse rate in the n-3 treated patients and controls (RR 1.02; 95% CI 0.51 to 2.03; P = 0.96). Combining the studies resulted in virtually no statistical heterogeneity (P = 0.93, I(2) = 0%). Various subgroup and sensitivity analyses showed similar results. However, the total number of patients enrolled in these studies was small (n = 138). No significant adverse events were recorded in any of the studies and not enough data were available to pool the other secondary outcomes for meta-analysis. No evidence was found that supports the use of omega 3 fatty acids for maintenance of remission in UC. Further studies using enteric coated capsules may be justified.

Dichi I. et al (2000) reported that fish oil omega-3 fatty acids exert anti-inflammatory effects on patients with ulcerative colitis. However, a comparative study in patients with mild to moderate ulcerative colitis receiving only sulfasalazine or omega-3 fatty acids has not been performed. We sought to detect changes in the inflammatory disease activity with the use of either fish oil omega-3 fatty acids or sulfasalazine in patients with ulcerative colitis. Ten patients (five male, five female; mean age = 48 +/- 12 y) with mild to moderate active ulcerative colitis were investigated in a randomized cross-over design. They received either sulfasalazine (2 g/d) or omega-3 fatty acids (5.4 g/d) for 2 m.o. Disease activity was assessed by clinical and laboratory indicators, sigmoidoscopy, histology, and whole-body protein turnover (with 15N-glycine). Treatment with omega-3 fatty acids resulted in greater disease activity as detected by a significant increase in platelet count, erythrocyte sedimentation rate, C-reactive protein, and total fecal nitrogen excretion. No major changes in protein synthesis and breakdown were observed during either treatment. In conclusion, treatment with sulfasalazine is superior to treatment with omega-3 fatty acids in patients with mild to moderate active ulcerative colitis.
Barbosa DS (2003) studied that the potential pathogenicity of free radicals may have a pivotal role in ulcerative colitis. Fish oil omega-3 fatty acids exert anti-inflammatory effects on patients with ulcerative colitis (UC), but the precise mechanism of the action of fish oil on oxidative stress is still controversial. The aim of the present work was to verify the blood oxidative stress in patients with UC and determine whether the association of sulfasalazine to fish oil omega-3 fatty acids is more effective than isolated use of sulfasalazine to reduce the oxidative stress.

Dichi I. and Stenson WF (2013) studied that fish oil supplements and omega-3 fatty acids have been studied for several years as a complementary or alternative treatment for IBD (Crohn’s disease in particular) with varying results. Some researchers suggest that fish oil may work by reducing existing inflammation but that fish oil is not necessarily effective in preventing inflammation. In one study, 59% of Crohn’s disease patients tested maintained their remission after taking fish oil supplements for one year compared to 26% in the placebo group. A second study showed that while taking fish oil supplements, ulcerative colitis patients were able to reduce their doses of prednisone. After stopping the fish oil, patients taking a placebo needed higher doses of prednisone again. A third study compared the effectiveness of sulfasalazine against fish oil for ulcerative colitis. Researchers found that sulfasalazine was more effective than fish oil in treating inflammation for people with mild to moderate ulcerative colitis.

Bahaa N., Soliman, Kalleny N. et al. (2010) studied that Ulcerative Colitis (UC) is an inflammatory bowel disease (IBD) well known by its exacerbated immune response. At present, a specific causal treatment for IBD is not available. The drugs currently used for management of IBD unfortunately are not devoid of potentially serious side effects. Polyunsaturated fatty acids (PUFAs) as omega-3 and omega-6 were reported to have immunomodulatory activities. Hence, may be of benefit in treating UC. The goal of the study was to illustrate the effect of omega-3 and omega-6 fatty acids on ulcerative colitis induced in male albino rat. Ulcerative colitis induction showed mucosal injury. There were patchy areas with loss of crypt architecture, inflammatory cell infiltrate and ulcerated mucosa. Scanning electron microscopic study revealed areas of ulceration. Whereas other areas showed alteration of the columnar absorptive cells. Transmission
electron microscopic study revealed loss of apical microvilli of enterocytes with signs of degeneration. Administration of omega-3 completely treated the colonic structure, while omega-6 was by far less efficient in treating induced ulcerative colitis. Omega-6 fatty acids partially improved the colon against ulcer induction. Meanwhile, omega-3 fatty acid proved to be a more effective dietary management of ulcerative colitis without the adverse effects of either surgery or medications.

Turner D, Steinhart H and Griffiths M (2007) reported that omega-3 fatty acid (n-3, fish oil) have been shown to anti-inflammatory properties. Therefore, n-3 therapy may be beneficial in chronic inflammatory disorders such as ulcerative colitis. Randomized placebo-controlled trials (RCT) of fish oil for maintenance of remission in UC were included. Studies must have enrolled patients (of any age group) who were in remission at the time of recruitment, and were followed for at least six months. The intervention must have been fish oil given in pre-defined dosage. Co-interventions were allowed only if they were balanced between the study groups. The primary outcome was relapse rate and the secondary outcome was frequency of adverse events. Other outcomes to assess efficacy were change in disease activity scores and time to first relapse. The three studies that were included used different formulation and dosing of n-3 but none used enteric coated capsules. The pooled analysis showed a similar relapse rate in the n-3 treated patients and controls (RR 1.02; 95% CI 0.51 to 2.03; P = 0.96). Combining the studies resulted in virtually no statistical heterogeneity (P = 0.93, I^2 = 0%). Various subgroup and sensitivity analyses showed similar results. However, the total number of patients enrolled in these studies was small (n = 138). No significant adverse events were recorded in any of the studies and not enough data were available to pool the other secondary outcomes for meta-analysis. No evidence was found that supports the use of omega-3 fatty acids for maintenance of remission in UC. Further studies using enteric coated capsules may be justified.

Calder P. (2006) studied that inflammation is part of the normal host response to infection and injury. However, excessive or inappropriate inflammation contributes to a range of acute and chronic human diseases and is characterized by the production of inflammatory cytokines, Arachidonic acid-derived eicosanoids (prostaglandins,
thromboxanes, leukotrienes, and other oxidized derivatives), other inflammatory agents (eg, reactive oxygen species), and adhesion molecules. At sufficiently high intakes, long-chain n-3 polyunsaturated fatty acids (PUFAs), as found in oily fish and fish oils, decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species and the expression of adhesion molecules. Long-chain n-3 PUFAs act both directly (eg, by replacing Arachidonic acid as an eicosanoid substrate and inhibiting Arachidonic acid metabolism) and indirectly (eg, by altering the expression of inflammatory genes through effects on transcription factor activation). Long-chain n-3 PUFAs also give rise to a family of anti-inflammatory mediators termed resolvins. Thus, n-3 PUFAs are potentially potent anti-inflammatory agents. As such, they may be of therapeutic use in a variety of acute and chronic inflammatory settings. Evidence of their clinical efficacy is reasonably strong in some settings (eg, in rheumatoid arthritis) but is weak in others (eg, in inflammatory bowel diseases and asthma). More, better designed, and larger trials are required to assess the therapeutic potential of long-chain n-3 PUFAs in inflammatory diseases. The precursor n-3 PUFA α-linolenic acid does not appear to exert anti-inflammatory effects at achievable intakes.

Maclean C. et al. (2005) studied that n-3 fatty acids are purposed to have health effects in patients with inflammatory bowel disease (IBD), but studies have reported mixed results. The available data are insufficient to draw conclusions about the effects of n-3 fatty acids on clinical endoscopic or histologic scores or remission or relapse rates.

Grimm H. et al. (2002) reported that over the last few years immunonutrition has gained increasing importance. Among other compounds lipids, especially n-3 polyunsaturated fatty acids were shown to influence the immune response. The anti-inflammatory effects they exert can be induced by free fatty acids, triglyceride fatty acids, after incorporation into the membrane phospholipid bilayer or following metabolism to eicosanoids. N-3 fatty acids influence inflammatory cell activation processes from signal transduction to protein expression even involving effects at the genomic level. N-3 fatty acid-mediated mechanisms decreased cytokine-induced adhesion molecule expression, thereby reducing inflammatory leucocyte-endothelium interactions and modified lipid mediator synthesis, thus influencing the transendothelial migration of leucocytes and leucocyte trafficking in
general. Even the metabolic repertoire of specific immunocompetent cells such as cytokine release or proliferation is modified by n-3 fatty acids. Beyond this they regulate lipid homeostasis shifting the metabolic pathways towards energy supply thus optimizing the function of immune cells. Due to the regulatory impact on different processes of inflammatory and immune cell activation n-3 fatty acids provide positive effects on various states of immune deficiencies and diseases with a hyper inflammatory character, among which selected examples are presented.

2.5.3 Studies on Probiotics:

Kalk E. (2004) reported that the probiotic drug E.coli Nissle 1917 shows efficacy and safety in maintaining remission equivalent to the gold standard mesalazine in patients with ulcerative colitis. The effectiveness of probiotic treatment further underlines the pathogenetic significance of the enteric flora.

Bibiloni R. (2005) reported that intestinal bacteria have been implicated in the initiation and perpetuation of IBD; in contrast, “probiotic bacteria” have properties possibly effective in treating and preventing relapse of IBD. The researcher evaluated the safety and efficacy of VSL #3 and the components, and the composition of the biopsy-associated microbiota in patients with active mild to moderate ulcerative colitis (UC). Treatment of patients with mild to moderate UC, not responding to conventional therapy, with VSL #3 resulted in a combined induction of remission/response rate of 77% with no adverse events. At least some of the bacterial species incorporated in the probiotic product reached the target site in amounts that could be detected.

Furrie E. (2004) studied that Ulcerative Colitis (UC) is an acute and chronic inflammatory disease of the large bowel with unknown aetiology. The immune response against normal commensal microorganisms is believed to drive inflammatory processes associated with UC. Therefore, modulation of bacterial communities on the gut mucosa, through the use of probiotics and prebiotics, may be used to modify the disease state. Short term symbiotic treatment of active UC resulted in improvement of the full clinical appearance of chronic inflammation in patients receiving this therapy.
Tursi A et al. (2004) reported that Balsalazide is well tolerated and effective in treating acute ulcerative colitis. VSL #3 is a probiotic cocktail proven to be effective in preventing flare-ups of chronic pouchitis. The researcher compared the efficacy and safety of low-dose balsalazide (2.25 g/day) plus 3 g/day VSL #3 (group A) with medium-dose balsalazide alone (group B) and with mesalazine (group C) in the treatment of mild-to-moderate active ulcerative colitis. Balsalazide/VSL #3 may be a very good choice in the treatment of active mild-to-moderate active ulcerative colitis instead of balsalazide alone or mesalazine.
Gionchetti P. et al. (2003) resulted that they have recently documented of a highly concentrated probiotic preparation (VSL #3) in the prevention of flare-up in patients with chronic pouchitis. The aim of this study was to compare probiotic therapy with VSL #3 versus placebo in the ability to prevent the onset of the acute pouchitis during the first year after ileal pouch-anal anastomoses. Treatment with VSL #3 is effective in the prevention of the onset of acute pouchitis and improves quality of life of patients with ileal pouch-anal anastomoses.

Miele E. (2009) reported that several probiotic compounds have shown promise in the therapy of ulcerative colitis (UC). However, a strong sustained benefit remains to be seen. Uncontrolled pilot studies suggest that a probiotic preparation (VSL #3) maintains remission in mild to moderate UC and reduces active inflammation in adult patients. Aims of the researcher’s prospective, 1- year, placebo-controlled, double-blind study were to assess the efficacy of VSL #3 on induction and maintenance of remission and to evaluate the safety and tolerability of the probiotic preparation therapy in children with active UC.

Tursi A. et al. (2010) studied that VSL #3 is a high-potency probiotic mixture that has been used successfully in the treatment of pouchitis. The primary end point of the study was to assess the effects of supplementation with VSL #3 in patients affected by relapsing ulcerative colitis (UC) who are already under treatment with 5-aminosalicylic acid (ASA) and/or immunosuppressants as stable doses. VSL #3 supplementation is safe and able to reduce UCDAI scores in patients affected by relapsing mild-to-moderate UC who are under treatment with 5-ASA and/or immunosuppressants. Moreover, VSL #3 improves rectal bleeding and seems to reinduce remission in relapsing UC patients after 8 weeks of treatment, although these parameters do not reach statistical significance.

Schultz M. and Sartor R. (2000) reported that the pathogenesis of inflammatory bowel diseases remains elusive. However, the resident luminal bacteria seem to be an important factor in their development and chronicity. There is evidence to suggest that inflammatory bowel diseases may represent an aggressive immunological response to the resident luminal flora, rather than alteration in the normal flora. In prior research,
probiotic bacteria were effective in managing certain acute diarrheal diseases and investigators reported that certain Lactobacilli strains seem to have protective immunomodulating and bowel flora manipulating properties. The researchers have reported that the results of recent studies with probiotics in animal models, in which promising effects for the treatment of chronic inflammatory bowel disease, pouchitis, and ulcerative colitis were observed. Future research may clarify a precise role for probiotic bacteria in managing chronic inflammatory bowel disease.

Rachmilewitz D. et al. (2004) tested that whether the attenuation of experimental colitis by live probiotic bacteria is due to their immunomodulatory DNA, whether toll-like receptor (TLR) signaling is required, and whether nonviable probiotics are effective. The protective effects of probiotics are mediated by their own DNA rather than by their metabolites or ability to colonize the colon. TLR9 signaling is essential in mediating the anti-inflammatory effect of probiotics, and live microorganisms are not required to attenuate experimental colitis because nonviable probiotics are equally effective.

Zocco M. et al. (2006) evaluated that Aminosalicylates are the mainstay of therapy to prevent relapse of quiescent ulcerative colitis. The rationale for using probiotics is based on the evidence implicating intestinal bacteria in the pathogenesis of this disorder. Lactobacillus GG seems to be effective and safe for maintaining remission in patients with ulcerative colitis, and it could represent a good therapeutic option for preventing relapse in this group of patients.

Mimura T. et al. (2003) studied that ten to 15% of patients with pouchitis experience refractory of recurrent disease. The aim of this study was to evaluate the effectiveness of a single daily high dose probiotic preparation (VSL #3) in maintaining antibiotic induced remission, and quality of life for one year in such patients. The once daily high dose probiotic VSL #3 is effective in maintaining antibiotic introduced remission for at least a year in patients with recurrent or refractory pouchitis. This is associated with a high level of quality of life.

Sood A. et al. (2009) reported that probiotics can maintain ulcerative colitis (UC) in remission effectively, but little is known of their ability to induce remission. The
researcher conducted a multicenter, randomized, double-blind, placebo-controlled trial of a high-potency probiotic, VSL #3, for the treatment of mild-to-moderately active UC. VSL #3 is safe and effective in achieving clinical responses and remission in patients with mild-to-moderately active UC.

Dr. Prantera C. et al. (2001) experimented that luminal bacteria may be involved in Crohn’s disease. Probiotics are a possible alternative to antibiotics. The aim of this randomized placebo controlled study was to determine if Lactobacillus GG, given by mouth for one year, could prevent Crohn’s recurrent lesions after surgery or to reduce their severity. Lactobacillus GG seems neither to prevent endoscopic recurrence at one year nor reduce the severity of recurrent lesions.

Karimi M. et al (2005) reported that Arthralgia is a common extraintestinal manifestation of inflammatory bowel disease (IBD). Alterations of the immunologic regulation in the gut may contribute to the pathogenesis of Arthralgia. Probiotics (VSL #3) have proven effective in the treatment of the pouchitis in patients with ileal pouch anal anastomoses after proctocolectomy for ulcerative colitis both in maintaining remission and in preventing a flare-up without side effects. The aim of this study was to determine the safety and efficacy of VSL #3 in patients with quiescent IBD who suffered from Arthralgia for more than two weeks. An open-label trial was conducted using VSL #3. Pre- and post-treatment joint pain intensity were measured on the Ritchie Articular Index and visual analog scale. Disease activity of the bowel was assessed by the Truelove-Witts and the Harvey-Bradshaw scores. Sixteen of 29 patients completed the trial; in 10 of the 16 patients’ statistically significant improvements was documented by the Ritchie Articular Index. No one of the patients had a relapse of intestinal disease while on probiotics. These preliminary results suggest that the probiotic mixture VSL #3 may be an alternative treatment for Arthralgia in patients with IBD without inducing exacerbation of the disease, because probiotics may be effective in the treatment of IBD as well, our results suggest that patients with active disease and Arthralgia may also derive benefit from this treatment. Proper randomized controlled studies are indicated.

Pena A.S. et al. (2004) reported that Crohn’s disease, ulcerative colitis, and pouchitis are caused by overly aggressive immune responses to a subset of commensal
(nonpathogenic) enteric bacteria in genetically predisposed individuals. Clinical and experimental studies suggest that the relative balance of aggressive and protective bacterial species is altered in these disorders. Antibiotics can selectively decrease tissue invasion and eliminate aggressive bacterial species or globally decrease luminal and mucosal bacterial concentrations, depending on their spectrum of activity. Alternatively, administration of beneficial bacterial species (probiotics), poorly absorbed dietary oligosaccharides (prebiotics), or combined probiotics and prebiotics (synbiotics) can restore a predominance of beneficial Lactobacillus and Bifidobacterium species. Current clinical trials do not fulfill evidence-based criteria for using these agents in inflammatory bowel diseases (IBD), but multiple nonrigorous studies and widespread clinical experience suggest that metronidazole and/or ciprofloxacin can treat Crohn’s colitis and ileocolitis (but not isolated ileal disease), perianal fistulae and pouchitis, whereas selected probiotic preparations prevent relapse of quiescent ulcerative colitis and relapsing pouchitis. These physiologic approaches offer considerable promise for treating IBD, but must be supported by rigorous controlled therapeutic trials that consider clinical disease before their widespread clinical acceptance. These agents likely will become an integral component of treating IBD in combination with traditional anti-inflammatory and immunosuppressive agents.

Seksik P. et al. (2002) studied that the colonic micro flora is involved in the pathogenesis of Crohn’s disease (CD) but less than 30% of the micro flora can be cultured. The researcher investigated potential differences in the faecal micro flora between patients with colonic CD in remission (n = 9), patients with active colonic CD (n = 8), and healthy volunteers (n = 16) using culture independent techniques. The biodiversity of the micro flora remains high in patients with CD. Enterobacteria were observed significantly more frequently in CD than in health, and more than 30% of the dominant flora belonged to yet underfined phylogenetic groups.
2.5.4 Studies on Various Herbs for the treatment of Ulcerative Colitis:

2.5.4.1 Woodfordia Floribunda (Dhataki):

Photo Courtesy: [www.ecoplanet.in](http://www.ecoplanet.in), Date: 25/09/2013, Time: 2:11 pm

Finose A. and Devaki K. (2011) studied that a preliminary phytochemical screening so as to detect the major class of compounds present. TLC profiling of the Woodfordia Floribunda flowers was carried out using sequential extracts of solvents with varying polarity; petroleum ether, chloroform and methanol respectively. The TLC documentation was done in short UV (254 nm), long UV (365 nm) and visible light after derivatisation with Anisaldehyde Sulphuric acid as the spray reagent. Then DPPH free radical scavenging assay was carried out in the flowers so as to detect its antioxidant activity. The flower has a significant sweetness when tasted; so the total estimation for the starch content in the plant was carried out. The HPLC studies were performed in the methanolic extract of the plant, since it gave better separation than the other two solvents. The results obtained can be used for the genuine identification of the plant from its adulterants.

Zaware B. et al. (2011) reported that the present work was undertaken to validate its folk use in the treatment of ulcerative colitis (UC) by using the method of acetic acid-induced colitis in mice. Ethanol extract (100 mg/kg) reduced the level of MPO in blood from 355 ± 0.39 to 240 ± 0.36 U/mL and from 385 ± 0.35 to 257 ± 0.36 U/mg in tissue. Similarly, it
reduced the level of MDA in blood from $9.40 \pm 0.42$ to $6.10 \pm 0.36$ nmol/mL and from $9.38 \pm 0.56$ to $5.89 \pm 0.56$ U/mg in tissue. Both the results are comparable with the standard drug, prednisolone (5 mg/kg). This preventive effect was observed by morphological and histopathological study. Results showed that ethanol extract of Woodfordia floribunda root is effective in the treatment of UC and results are comparable with the standard drug, prednisolone, and thus possessing a great potential in the treatment of UC.

Machana S. et al. (2012) evaluated the anticancer activity of the extract fraction of Woodfordia floribunda, Finet & Gagnep and the synergistic anticancer effect of the extracts from Woodfordia floribunda by using the ATR/FT-IR spectroscopy. The 50% ethanol-water crude leaf extract of Woodfordia was prepared and was further fractionated to isolate various fractions. The anticancer activity was investigated from cytotoxicity against HepG2 using a neutral red assay and apoptosis induction by evaluation of nuclei morphological changes after DAPI staining. Synergistic anticancer effects of the extracts from Woodfordia floribunda were performed using the ATR/FT-IR spectroscopy. The result showed that the EW-L showed higher cytotoxicity and apoptosis induction in HepG2 cells than its fractionated extracts. The hexane extract exhibited higher cytotoxicity and apoptosis induction than the water extracts, but less than the EW-L. The combined water and hexane extracts apparently increased cytotoxicity and apoptosis induction. The % apoptotic cells induced by the extract mixture were increased about 2-fold compared to the single hexane extract. The polar extract fraction is necessary for the anticancer activity of the non-polar extract fraction. The ATR/FT-IR spectra illustrates the physical interaction among the constituents in the extract mixture and reveals the presence of polyphenolic constituents in the EW-L, which might play a role for the synergistic anticancer effect.

Gulati K. et al. (2012) studied the traditional Indian system of medicine (Ayurveda) describes different modalities involved in the prevention and treatment of disease and stresses upon the role of diet, life style and drugs as cornerstones of therapy. Medicinal plant products are known to modify different aspects of human physiology and exert an alleviating influence on several pathophysiological states, and concepts of immunity and
immunomodulation can be traced back several hundred years to the history of medicine. However, it is only in recent years that the scientific concept of immunomodulation has been forwarded, and it now appears that some of the beneficial effects of Indian medicinal plants, proposed in Ayurveda by Charaka and Sushruta Samhita, may be due to these "immunomodulatory" effects. Several research groups have worked on the scientific basis of such immunomodulatory effects of plant products, and as a result, considerable data has accrued. The present review summarizes some of these experimental data in an attempt to justify some of their beneficial effects in health and disease, and also to provide insights into the future research in this area.

Thatte U. (2011) the flowers of dhataki are used for the medicinal purpose. It is used both internally as well as externally. The powder of its dried flowers is sprinkled on the wounds to alleviate the burning sensation, arrest the bleeding and to promote the healing. The fine powder of its dried flowers, mixed with sesame oil, is applied on the burns and scalds. The juice of its fresh flowers applied on the forehead, reduces the headache, especially, due to pitta. To facilitate the dental eruption in children, the powder of its dried flowers is massaged on the gums. Internally, dhataki is beneficial in a vast range of diseases. It is a powerful astringent, hence works well in diarrhea, dysentery and piles, associated with bleeding. A mixture of dhataki powder, honey and rice water is extremely effective in diarrhea, dysentery, piles, menorrhagia and raktapitta to arrest the bleeding. It can be safely used even in pregnancy, associated with such ailments. In chronic diarrhea, dhataki flowers combined with mocarasa and indrayava is a very effective medicament. The flowers of dhataki are most commonly used in Ayurvedic pharmacy to facilitate fermentation in the manufacture of asavas and aristas as they contain yeast. The decorations of its flowers effectively quench the excessive thirst, especially in diabetic patients. Being mutra virajaniya in property, it helps to bring back the color of urine to normal one, especially in diabetes. The jam (avaleha) prepared of its flowers, helps in controlling bleeding in menorrhagia as well as it alleviates the leucorrhoea. The powder of its dried flowers is beneficial, as an adjuvant, in the heart diseases. Dhataki is also used to alleviate the fever due to pitta.
2.5.4.2 Aegle Marmelos (Bael Fruit):

![Figure No: 17](image)

Photo Courtesy: [www.satvikshop.com](http://www.satvikshop.com), Date: 25/09/2013, Time: 2:17 pm

Playford R. J. (2003) studied that many healthy subjects and patients are taking natural bioactive products for the prevention and treatment of multiple conditions, including gastrointestinal disorders. Based on current evidence, the scientific validity of the use of many of these commercial compounds by the general public is several limited, with quality control and regulatory issues continuing to be a concern. Nevertheless, there is sufficient preliminary data to warrant further research of these products in order to identify novel compounds for potential clinical use in addition to performing formal randomized controlled clinical trials of the commercial preparations.

Langmead L. and Rampton D.S. (2001) studied that herbal medicines are now used by up to 50% of the western population, in a substantial minority of instances for the treatment or prevention of digestive disorders. Although most indications for the use of such remedies are anecdotally or traditionally derived, controlled trials suggest some benefits for ginger in nausea and vomiting, liquorice extracts in peptic ulceration, Chinese herbal medicine in irritable bowel syndrome, opium derivatives in diarrhea and senna, isaphagula and sterculia in constipation. Herbal preparations contain many bioactive compounds with potentially deleterious as well as beneficial effects. There is clearly a
need for greater education of patients and doctors about herbal therapy, for legislation to control the quality of herbal preparations, and in particular for further randomized controlled trials to establish the value and safety of such preparations in digestive and other disorders.

Bhat H., Joseph N. and Fazal F. (2011) studied that Aegle Marmelos, a plant indigenous to India has been used by the inhabitants of the Indian subcontinent for over 5000 years. The leaves, bark, roots, fruits and seeds are used extensively in the Indian traditional system of medicine the ayurveda and in various folk medicine to treat myriad ailments. Bael fruits are also used in the treatment of chronic diarrhea, dysentery, and peptic ulcers, as a laxative and to recuperate from respiratory affections in various folk medicines. Scientific studies have validated many of the ethnomedicinal uses and reports indicate that the fruit possesses broad range of therapeutic effects that includes free radical scavenging, antioxidant, inhibition of lipid peroxidation, antibacterial, antiviral, anti-diarrheal, gastroprotective, anti-ulcerative colitis, hepatoprotective, anti-diabetic, cardioprotective and radioprotective effects. For the first time this review critically assesses the nutritional values, phytochemistry and preclinical pharmacological properties of the bael fruit. Attempts are also made at emphasizing the dietary and pharmaceutical potential of bael fruit that has been largely underutilized and neglected.

Vishwanath M. et al. (2012) studied to elucidate the ameliorative effect of aqueous extract of fruit of Cucumis sativus (C.Sativus) (CS) in acetic acid induced colitis in wistar rats. Intrarectal instillation of acetic acid caused enhanced ulcer area, ulcer index, and spleen weight, colon weight to length ratio, colonic MPO and hematological parameters. Pretreatment with C.Sativus for 7 d exhibited significant effect in lowering of ulcer area, ulcer index as well as neutrophil infiltration at a dose of 250 and 500 mg/kg in acetic acid induced colitis. The present investigation demonstrates C.Sativus is of potent therapeutic value in the amelioration of experimental colitis in laboratory animals by inhibiting the inflammatory mediator.

Romano M. et al. (2012) studied that natural medicinal products have been used for millennia for the treatment of several ailments. Although many have been supervised by conventional pharmaceutical approaches, there is currently resurgence in the interest in
natural products by the general public and the use of complementary and alternative medicine is increasing rapidly in developed countries. Also, pharmaceutical industries are more and more interested in examining their potential as sources of novel medicinal compounds which may act as growth factor or show immunomodulatory or antimicrobial activity. The subgroup of natural bioactive compounds that bridge the gap between food products and drugs are termed neutraceuticals or functional foods. In contrast with most standard medicinal compounds, neutraceuticals are generally used to prevent rather than to treat disease. Many of the claims for such products are supported by very limited scientific evidence. However, there has recently been a great interest at evaluating the mechanism by which natural products exert their beneficial effects in the gastrointestinal tract. In particular, a major area of interest is for the use of biologically active chemical components of plants, i.e. phytochemicals, in a number of gastrointestinal disorders. While the major focus of phytochemical research has been on cancer prevention, several products of plant origin are being used and/or under study for a variety of other gastrointestinal problems. In this review the researcher discuss the scientific evidence supporting the potential use of neutraceuticals as agents capable to prevent or accelerate healing of gastrointestinal mucosal damage, with a focus on polyphenol extracts obtained from apple.

Awaad A., El-Meligy R. and Soliman G. (2013) studied that ulcerative colitis is an inflammatory chronic disease that affects the mucosa and submucosa of the colon and rectum. Several types of drugs are available such as aminosalicylates. Peptic ulcer disease (PUD) is a common disorder that affects millions of individuals worldwide and it can be considered one of the most important common diseases in the world. Treatment of peptic ulcers depends on using a number of synthetic drugs that reduce the rate of stomach acid secretion (Antacids), protect the mucous tissues that line the stomach and upper portion of the small intestine (Demulcents) or to eliminate Helicobacter pylori (H.Pylori). In most cases, incidence of relapses and adverse reactions is seen in the following synthetic antiulcer therapy. Accordingly, the main concern of the current article is to introduce a safe drug (or more) of natural origin, to be used for the management of gastric ulcers without side effects. A widespread search has been launched to identify new anti-ulcer therapies from natural sources. Herbs, medicinal plants, spices, vegetables and crude drug
substances are considered to be a potential source to control various diseases including gastric ulcer and ulcerative colitis. In the scientific literature, a large number of medicinal plants and their secondary metabolites with potential anti-ulcer (anti-peptic ulcer and antiulcerative colitis) activities have been reported. Treatment with natural products produces promising results and fewer side effects. The researcher’s goal is to collect the published data in the last 24 years and reviews the natural products reported in the treatment of these diseases and their mechanism of action.

2.5.4.3 Bombax Malabaricum (Salmali) :

![Figure No 18](https://www.googleimages.com)

Jagtap AG, Niphadkar PV and Phadke AS (2011) studied that there is a little evidence regarding role of Bombax malabaricum in the treatment of inflammatory bowel disease (IBD); though it is clinically employed as a constituent of a polyherbal preparation for IBD. To establish its role as a monotherapy for IBD, preliminary phytochemical screening of aqueous extract of B. malabaricum (AEBM) was undertaken. Subsequently, its protective effect in indomethacin and iodoacetamide induced colitis in rats (45, 90, 180, 270 mg/kg) and acetic acid induced colitis in mice (65, 130, 250, 500 mg/kg) was assessed. AEBM (270 mg/kg) in indomethacin and iodoacetamide induced colitis significantly reduced the ulcer score and myeloperoxidase (MPO) activity. AEBM/500
mg/kg dose/significantly reduced the ulcer score and MPO activity in acetic acid induced colitis. The extract (270 mg/kg in rats and 500 mg/kg in mice) was found to be comparable with prednisolone (10 mg/kg) and 5-aminosalicylic acid (5-ASA) (100 mg/kg) used as standard treatments. AEBM provided reduction in a dose dependent manner. AEBM (500 mg/kg) significantly reduced colonic and serum TNF-α level when compared with the positive control in acetic acid induced colitis model. The results suggest a protective role of AEBM in IBD.

Kandhare et al. (2012) studied to elucidate the ameliorative effect of hydrochloric acid extract of leaves of Bombax malabaricum in acetic acid induced experimental colitis in male wistar rats and the present investigation demonstrates BM is of potent therapeutic value in the amelioration of experimental colitis in laboratory animals by inhibiting the proinflammatory mediator like nitric oxide and TNF-α.

Vishwanath M. et al (2012) studied that to elucidate the ameliorative effect of aqueous extract of fruit of Bombax malabaricum in acetic acid induced colitis in Wistar Rats. Intrarectal installation of acetic acid caused enhanced ulcer area, ulcer index, and spleen weight, colon weight to length ratio, colonic MPO and hematological parameters. Pretreatment with Bombax malabaricum for 7 days exhibited significant effect in lowering of ulcer area, ulcer index as well as neutrophil infiltration at a dose of 250 and 500 mg/kg in acetic acid induced colitis.

Debnath T. et al (2013) studied that accumulating epidemiological and clinical study indicates that inflammation is a significant risk factor to develop various human diseases such as inflammatory bowel disease (IBD), chronic asthma, rheumatoid arthritis, multiple sclerosis and psoriasis. Suppressing inflammation is therefore important to control or prevent various diseases. Among them, IBD is one of the major problems affecting people worldwide. IBD affects at least one in a thousand persons in many western countries. Various natural products have been shown to safely suppress pro-inflammatory pathway and control IBD. In vivo and/or in vitro studies indicate that anti-IBD effects of natural products occur by inhibition of the expression of pro-inflammatory cytokines (for example, tumor necrosis factor-α (TNF-α), intracellular adhesion molecule expression and pro-inflammatory mediators (such as inducible nitric oxide synthase (iNOS) and
cyclooxygenase 2 (COX2), master transcription factors (such as nuclear factor -κB (NF-κB)), reactive oxygen species (ROS) and by improving the antioxidant activity, in this review, we summarize recent research focused on IBD and the effects that natural products have on IBD factors.

Hur S. et al. (2012) studied that the purpose of this review is to provide an overview of the effects that natural products have on inflammatory bowel disease (IBD) and to provide insight into the relationship between these natural products and cytokines modulation. More than 100 studies from the past 10 years were reviewed herein on the therapeutic approaches for treating IBD. The natural products having anti-IBD actions included phytochemicals, antioxidants, microorganisms, dietary fibers, and lipids. The literature revealed that many of these natural products exert anti-IBD activity by alerting cytokine production. Specifically, phytochemicals such as polyphenols or flavonoids are the most abundant, naturally occurring anti-IBD substances. The anti-IBD effects of lipids were primarily related to the n-3 polyunsaturated fatty acids. The anti-IBD effects of phytochemicals were associated with modulating the levels of tumor necrosis factor α (TNF-α), interleukin (IL)-interleukin 1, IL-6, inducible nitric oxide synthase, and myeloperoxide. The anti-IBD effects of dietary fiber were mainly mediated via peroxisome proliferator–activated receptor-γ, TNF-α, nitric oxide, and IL-2, whereas the anti-IBD effects of lactic acid bacteria were reported to influence interferon-γ, IL-6, IL-12, TNF-α, and nuclear factor-κ light-chain enhancer of activated B cells. These results suggest that the anti-IBD effects exhibited by natural products are mainly caused by their ability to modulate cytokine production. However, the exact mechanism of action of natural products for IBD therapy is still unclear. Thus, future research is needed to examine the effect of these natural products on IBD and to determine which factors are most strongly correlated with reducing IBD or controlling the symptoms of IBD.

Dey A. and Nath J. (2012) studied that an ethno botanical survey was conducted in the remote hills, forests and rural areas of Purulia, one of the tribal rich districts of the West Bengal state of eastern India. Purulia is a part of the biogeographic zone Deccan Peninsula Chhotonagpur. The authors have reported the use of medicinal plants by nine tribes of the district against various gastrointestinal disorders. A total number of 56 plants
belonging to 29 families have been reported to be used against different types of gastrointestinal disorders viz. indigestion, stomach pain, vomiting tendency, constipation, piles, diarrhea, dysentery, cholera, loss of appetite, liver complaints, intestinal worms etc. Fabaceae and Apocynaceae were found to be the dominant families of medicinal plants used to treat such ailments. Age, gender, literacy and profession of the aboriginals were found to be the significant factors when the traditional knowledge of medicinal botanicals was concerned. Due to urbanization and loss of biodiversity, the authors have noted a significant decrease in the ethnic knowledge as well as the botanicals. Preservation of folklore should be given utmost importance in this region to prevent the rapid loss of ethno botanical wealth.

2.5.4.4 Caryophyllus Aromaticus (Cloves) :

Figure No19

Dr. Sateesh s. et al. (2013) studied the analgesic effect of Caryophyllus aromaticus (flower buds) by formalin test in albido rats. Caryophyllus aromaticus 300 mg/kg significantly decreased the reaction time of early phase in formalin test similar to Pethidine whereas the combination of Naloxone and Caryophyllus aromaticus 300 mg/kg increased the reaction time of early phase, indicating that Naloxane inhibits the analgesic effect of Caryophyllus aromaticus. Caryophyllus aromaticus 300 mg/kg significantly decreased the reaction time of late phase also. Caryophyllus aromaticus (flower buds)
possesses significant central and peripheral analgesic activity and acts through opioid receptors.

Mathiazhagan S. et al. (2013) has been studied that Caryophyllus aromaticus mill L (Caryophyllus aromaticus) is a herbal spice plant that has several therapeutic effects. It also heals depression, grief, nervous stress and tension. In the present study we evaluated antidepressant-like effect of Caryophyllus aromaticus using forced swimming test (FST). The results showed that higher dose (200 mg/kg) of extract significantly increased swimming time and decreased immobility time. However, the two lower doses of extract (50 and 100 mg/kg) also had significant effect on these parameters. These results proposed antidepressant-like effect of higher dose concentration of ethanolic extract of Caryophyllus aromaticus.

Kumari MV (2013) studied that modulatory effects observed due to clove administration (0.5%, 1% and 2% w/w in the diet) to Swiss albino mice for 10, 20 and 30 days in the hepatic levels of cytochrome P-450 (Cyt. P-450), cytochrome b5 (Cyt. b5), aryl hydrocarbon hydroxylase (AHH), glutathione S-transferase (GST), DT-diaphorase (DTD), acid soluble sulfhydryl (SH) content and radiation-induced malondialdehyde (MDA) formation were recorded. Enhanced GST, Cyt. b5 and SH levels were observed in all the treatment groups, excepting those maintained on a 0.5% diet for 10 days which did not show significant increase in the GST and SH levels as compared to their respective controls. Significant reduction in Cyt. P-450 and MDA levels were observed in all groups at 30 days duration. While AHH levels remained unaltered by clove administration, DTD activity was elevated by 1% and 2% clove diets at 30 days duration. An in vivo bone marrow micronucleus assay demonstrated that administration of 0.5% and 2% clove diets for 10 days neither significantly induced micronuclei nor could effectively modulate the 7, 12-dimethylbenz[a]anthracene genotoxicity in mice. The results suggest whole cloves as potential chemopreventive agents.

Dr. Anand S. (2007) Clove (Caryophyllus aromaticus L.) has been used for clinical procedures. Blood constituents labeled with technetium-99m (99mTc) are used in nuclear medicine. The aim of this work was to evaluate the effects of clove extract on the
labeling blood constituents with 99mTc and on the morphology of red blood cells. Blood samples were incubated with clove, stannous chloride and 99mTc. Plasma, blood cells, insoluble fractions of plasma and blood cells were separated. The radioactivity was counted and percentage of radioactivity (%ATI) to each blood fraction was calculated. The shape and morphometric parameter (perimeter/area ratio) were evaluated. Clove extract altered significantly (p<0.05) the %ATI of blood constituents and the shape of red blood cells without modifying the perimeter/area ratio. The results indicate that clove extract presents chemical compounds that interfere with the radio labeling of blood constituents and alter the morphology of red blood cells by oxidative/chelating actions or interacting with the cellular membrane structure.

Misharina T. and Samusenko A. (2008) studied that antioxidant properties of individual essential oils from lemon (Citrus Limon L.), pink grapefruit (Citrus paradisi L.), coriander (Coriandrum sativum L.), and clove (Caryophyllus aromaticus L.) buds and their mixtures were studied by capillary gas-liquid chromatography. Antioxidant activity was assessed by oxidation of the aliphatic aldehyde hexanal to the carboxylic acid. The lowest and highest antioxidant activities were exhibited by grapefruit and clove bud essential oils, respectively. Mixtures containing clove bud essential oil also strongly inhibited oxidation of hexanal. Changes in the composition of essential oils and their mixtures in the course of long-term storage in the light were studied. The stability of components of lemon and coriander essential oils in mixtures increased compared to individual essential oils.

Ushimaru P. et al. (2007) reported that the present study aimed at evaluating the in vitro antimicrobial activity of methanolic extracts of some medicinal plants against Escherichiacoli, Salmonella Typhimurium, Staphylococcusauereus and Enterococcus sp. The methanolic extract of Caryophyllus aromaticus presented the highest anti-S. aureus activity and was effective against all bacterial strains tested. Comparisons with pertinent data from literature indicate that, according to the methodology adopted in studies on antimicrobial activity, the most diverse results can be obtained. Plant extracts have shown inhibitory effect on the growth of the bacteria studied, although of distinct
forms. It is therefore recommended that the nature and the number of the active antibacterial principles involved in each plant extract be studied in detail.

2.5.4.4 Holarrhena Antidysentrica (Kutaja):

Figure No: 20

Photo Courtesy: www.mobsea.co.in, Date: 25/09/2013, Time: 2:28 pm

Kavitha D. Shilpa PN and Devaraj SN (2004) studied that the alkaloids from the ethanolic extract of H. Antidysentrica seeds were evaluated for their antibacterial activity against clinical isolates of enteropathogenic Escherichia coli (EPEC) in vitro, and their antidiarrhoeal activity on castor oil-induced diarrhoea in rats, in vivo. The plasmid DNA, whole cell lysate and outer membrane protein profile of a clinical isolate of EPEC was determined in presence of alkaloids of H.antidysenterica. The disc diffusion and agar well diffusion methods were used to evaluate the antibacterial efficacy. The alkaloids showed strong antibacterial activity against EPEC strains. In castor oil-induced diarrhoea, alkaloids reduced the diarrhoea with decrease in the number of wet faeces in pre-treated rats at a dose of 200-800 mg/kg. The loss of plasmid DNA and suppression of high molecular weight proteins were observed on alkaloids treatment. Taking into account the multiple antibiotic
resistance of EPEC, the results suggest usefulness of alkaloids of H.antidysenterica seeds as antibacterial and antidiarrhoeal agents.

Rani P and Khullar N. (2004) studied that the screening was done of some plants of importance in the Ayurvedic system of traditional medicine used in India to treat enteric diseases. Fifty four plant extracts (methanol and aqueous) were assayed for their activity against multi-drug resistant Salmonella typhi. Strong antibacterial activity was shown by the methanol extracts of Aegle marmelos, Salmalia malabarica, Punica granatum, and Myristica fragrans, Holarrhena Antidysentrica, Terminalia Arjuna and Triphal (mixture of Emblica officinalis, Terminalia chebula and Terminalia belerica). Moderate antimicrobial activity was shown by Picorhiza kurroa, Acacia catechu, Acacia nilotica, Cichorium intybus, Embelia ribes, Solanum nigrum, Carum copticum, Apium graveolens, Ocimum sanctum, Peucedanum graveolens and Butea monosperma.

Ali KM et al. (2009) studied that the present study reports the effects of aqueous extract of seed of Holarrhena Antidysentrica for the management of streptozotocin (STZ) induced diabetes in rat. For the management of the carbohydrate metabolism in diabetes by the said extract, the activities of carbohydrate metabolic enzymes like glucose-6-phosphatase, glucose-6-phosphate dehydrogenase and hexokinase in liver along with quantification of glycogen in liver and skeletal muscle were measured and noted a significant recovery in respect to diabetic control group. As hyperlipidemia is one of the disorders of diabetes so, we have also assessed the serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDLc), very low density lipoprotein cholesterol (VLDLc) and high density lipoprotein cholesterol (HDLc). The said aqueous extract also resulted a significant recovery in the levels of above mentioned biosensors of lipid profile when treated to experimentally induce diabetic rat. The extract has no toxic effect in general which has been focused here by the monitoring of GOT and GPT activities in liver and kidney. The results of this study enlightened that the aqueous extract of said plant part has both antidiabetic and antihyperlipidemic activities.

Ahmad I and Beg A. (2001) studied the ethanolic extracts of 45 Indian medicinal plants traditionally used in medicine were studied for their antimicrobial activity against certain drug-resistant bacteria and a yeast Candida albicans of clinical origin. Of these, 40 plant
extracts showed varied levels of antimicrobial activity against one or more test bacteria. Anticandidal activity was detected in 24 plant extracts. Overall, broad-spectrum antimicrobial activity was observed in 12 plants (L. inermis, Eucalyptus sp., H. Antidysentrica, H. indicus, C. equistifolia. T. bekerica, T. chebula, E. officinalis, C. sinensis, S. aromaticum and P. granatum). No correlation was observed between susceptibility of test strains with plant extracts and antibiotic resistance behaviour of the microbial strains (Staphylococcus aureus, Salmonella paratyphi, Shigella dysenteriae, Escherichia coli, Bacillus subtilis, and Candida albicans). Qualitative phytochemical tests, thin layer chromatography and TLC-bioautography of certain active extracts demonstrated the presence of common phytocompounds in the plant extracts including phenols, tannins and flavonoids as major active constituents.

Raha S. and Roy S. (2001) studied that an efficient, rapid and large-scale propagation of the woody, aromatic and medicinal shrub, Holarrhena Antidysentrica, through *in vitro* culture of nodal segments with axillary buds, is described. N⁶-benzyladenine used at 15 μM was the most effective in inducing bud break and growth, and also in initiating multiple shoot proliferation at the rate of 43 microshoots per nodal explant with axillary buds, after 30 d of culture. By repeated sub culturing of nodal explants with axillary buds, a high-frequency multiplication rate was established. Efficient rooting was achieved with 35 μM indole-3-butyric acid which was the most effective in inducing roots, as 80% of the microshoots produced roots. Plantlets went through a hardening phase in a controlled plant growth chamber; prior to ex vitro transfer Micro propagated plants established in garden soil were uniform and identical to donor plants with respect to growth characteristics and vegetative morphology.
2.5.4.6 Cyperus Rotundus (Nut Grass):

Figure No: 21

Photo Courtesy: www.completewellbeing.com, Date: 29/10/2013, Time: 2:25 pm

Sonwa M. and Konig W. (2011) studied that minor constituents of the essential oil of Cyperus Rotundus have been investigated. The three new sesquiterpene hydrocarbons (−)-isorotundene, (−)-cypera-2, 4(15)-diene, (−)-nor rotundene and the ketone (+)-cyperadione were isolated and their structures elucidated. The absolute configuration of (−)-rotundene was derived by chemical correlation and enantio selective gas chromatography.

Seo W. et al. (2001) studied that the rhizomes of Cyperus Rotundus (C. Rotundus) have been used in oriental traditional medicines for the treatment of stomach and bowel disorders, and inflammatory diseases. Nitric oxide (NO) and superoxide (O$_2^-$) are important mediators in the pathogenesis of inflammatory diseases. This study was undertaken to address whether the methanol (MeOH) extract of rhizomes of C. Rotundus could modulate NO and O$_2^-$ productions by murine macrophage cell line, RAW 264.7 cells. The MeOH extract of rhizomes of C. Rotundus showed the inhibition of NO production in a dose-dependent manner by RAW 264.7 cells stimulated with interferon-γ plus lipo polysaccharide. The inhibition of NO production by the extract was due to the suppression of iNOS protein, as well as iNOS mRNA expression, determined by Western
and Northern blotting analyses, respectively. In addition, the MeOH extract suppressed the production of O$_2^-$ by phorbol ester-stimulated RAW 264.7 cells in dose- and time-dependent manners. Collectively, these results suggest that the MeOH extract of rhizomes of *C. Rotundus* could be developed as anti-inflammatory candidate for the treatment of inflammatory diseases mediated by overproduction of NO and O$_2^–$.

Suwunnamek U. and Parker C. (1975) studied that Glyphosate was applied to *Cyperus Rotundus* L. in combination with a range of other herbicides and certain non-herbicidal additives. Most herbicides tended to have an antagonistic effect with glyphosate, especially those which inhibit photosynthesis. On the other hand 2,4-D amine and amino triazole showed at least additive and sometimes synergistic effects. Striking activation was obtained with ammonium sulphate added at rates between 1·25 and 10 kg/ha. Other compounds causing almost equal activation were several ammonium phosphates, ammonium butyl-phosphate and urea. The activity of glyphosate on *C. Rotundus* was considerably greater when applied 3 weeks after planting than at 9 weeks. The activation was also greater at 3 weeks but was still apparent at 9 weeks.

Kilani S. et al. (2011) studied essential oil from the tubers of *Cyperus Rotundus*, obtained by steam distillation, and were analyzed by GC and GC/MS. In total, 33 compounds were identified. The oil was characterized by its high content of sesquiterpene with cyperene (30.9%) being major. The antibacterial activity of oil from tubers of *Cyperus Rotundus*, showed more important activity against Gram-positive bacteria specially *Staphylococcus aureus* than Gram-negative bacteria. The Antimutagenic activity was tested by the “SOS Chromotest” and the “Ames” test. *C. Rotundus* oil acted as an antimutagen against Aflatoxin B1 in both *Salmonella* strains (TA100 and TA98) and *Escherichia coli* strain (PQ37) and against nifuroxazide in *Escherichia coli* strain (PQ37), where its mutagenicity is not expressed. The highest rates of AFB1 mutagenesis inhibition tested by Ames assay, ranged from about 82.56% for TA100 strain to 85.47% for TA98 strain at the same dose of 50 μg AFB1 per plate. Whereas, the mutagenic effect of respectively nifuroxazide and AFB1 (50 μg/assay) were reduced by approximately 58.19% and 81.67% when tested by the SOS chromotest assay.
Jagtap AG, Shirke SS and Phadke AS (2004) a polyherbal ayurvedic formulation from an ancient authentic classical text of ayurveda was evaluated for its activity against inflammatory bowel disease (IBD). The polyherbal formulation contained four different drugs viz., Bilwa (Aegle marmelos), Dhanyak (Coriandrum sativum), Musta (Cyperus Rotundus) and Vala (Vetiveria zinzanioids). The formulation has been tried before in clinical practice and was found to be useful in certain number of cases of IBD (ulcerative colitis), so was tried in the same form i.e., decoction (aqueous extract) in experimental animals to revalidate the claims of the same. The formulation was tried on two different experimental animal models of inflammatory bowel disease, which are acetic acid-induced colitis in mice and indomethacin-induced enterocolitis in rats. Prednisolone was used as the standard drug for comparison. The formulation showed significant inhibitory activity against inflammatory bowel disease induced in these experimental animal models. The activity was comparable with the standard drug prednisolone. The results obtained established the efficacy of this polyherbal formulation against inflammatory bowel diseases.

Patel M. Patel K. and Gupta SN (2010) Ulcerative colitis is a chronic idiopathic inflammatory bowel disease with a relapsing nature. It is a very challenging disease affecting a patient during the most active period of his life i.e. 20 to 40 years of age. The main features are ano-rectal bleeding with increased frequency of bowel evacuation, general debility and with abnormal structural pathology in the descending colon, particularly sigmoid colon. In modern medical science, there is no permanent curative and safe treatment for this disease. This study can be helpful for reducing the need of steroids and surgical processes in the patients of ulcerative colitis. A clinical study of 43 patients of ulcerative colitis has been conducted at the O.P.D. (outdoor patient department) and I.P.D. (indoor patient department) of the P D Patel Ayurveda Hospital, Nadiad. They were given Udumbara kvatha basti with oral Ayurveda medicaments including Kutaj ghan vati, Udumbara kvatha, and combination of Musta, Nagakesara, Lodhra, Mukta panchamrut rasa for a one-month period. Results were analyzed statistically by using the ‘t’ test. In this study, it was observed that the symptoms and signs, daily dose of steroids and other anti-inflammatory drugs were reduced by more than 75% with a highly significant result. The hemoglobin level was also increased.
2.5.4.7 Withania Somnifera (Ashwagandha):

Figure No: 22

Elaskka M. et al (2004) studied that Withania Somnifera also known as Ashwagandha, Indian ginseng, and winter cherry, has been an important herb in the ayurvedic and indigenous medical systems for over 300 years. Historically, the plant has been used as an aphrodisiac, liver tonic, anti-inflammatory agent, astringent, and more recently to treat bronchitis, asthma, ulcers, emaciation, insomnia, and senile dementia. Clinical trials and animal research support the use of Ashwagandha for anxiety, cognitive and neurological disorders, inflammation, and Parkinson’s disease. Ashwagandha’s chemopreventive properties make it a potentially as an adaptogen for patients undergoing radiation and chemotherapy, Ashwagandha is also used therapeutically as an adaptogen for patients with nervous exhaustion, insomnia, and debility due to stress, and as an immune stimulant in patients with low white blood cell counts.

Bhattacharya SK and Muruganandam AV (2003) studied that Withania Somnifera (WS) Dunal is classified in Ayurveda, the ancient Hindu system of medicine, as arasayana, a group of plant-derived drugs reputed to promote physical and mental health, augment resistance of the body against disease and diverse adverse environmental factors, revitalize the body in debilitated conditions and increase longevity. These
attributes are remarkably similar to the properties ascribed to adaptogen like Panax ginseng (PG) in contemporary medicine. As such, the Adaptogenic activity of a standardized extract of WS roots was investigated against a rat model of chronic stress (CS). The stress procedure was mild, unpredictable foot shock, administered once daily for 21 days to adult male Wistar rats. CS induced significant hyperglycemia, glucose intolerance, and increase in plasma corticosterone levels, gastric ulcerations, male sexual dysfunction, cognitive deficits, immunosuppression and mental depression. These CS induced perturbations were attenuated by WS (25 and 50 mg/kg po) and by PG (100 mg/kg po), administered 1 h before foot shock for 21 days. The results indicate that WS, like PG, has significant antistress Adaptogenic activity, confirming the clinical use of the plant in Ayurveda.

Pawar P. et al. (2011) studied that Inflammatory Bowel Disease (IBD) is marked with chronic inflammation of intestinal epithelium driven by oxidative stress. Traditional treatments with plant extracts gained renewed interest due to their ability to ameliorate the multi factorial conditions like inflammation. We investigated the beneficial effects of Withania Somnifera in Trinitro Benzyl Sulfonyl Acid (TNBS) induced experimental IBD through a rectally applicable formulation. The extract, at 500 μg/ml, the highest concentration tested, showed 95.6% inhibition of lipid peroxidation, 14.8% NO scavenging, 81.79% H$_2$O$_2$ scavenging and a reducing capacity of 0.80. The results were comparable with standard antioxidants, ascorbic acid and curcumin. WSRE treatment positively scored on histopathological parameters like necrosis, edema, and neutrophil infiltration. The post treatment intestinal features showed restoration at par with the healthy intestine. In view of these results, gel formulation containing an aqueous extract of W. Somnifera, prepared for rectal application was tested for its anti-inflammatory activity in TNBS-induced rat models for IBD. Commercially available anti-inflammatory drug Mesalamine was used as the standard in this assay. Dose of the rectal gel applied at 1000 mg of WSRE per kg rat weight showed significant muco-restorative efficacy in the IBD-induced rats, validated by histo-pathological studies.

Shirin K. et al. (2010) studied that Withania Somnifera (family Solanaceae) has been studied to determine major and trace elements and their possible correlation with therapeutic value of the plant. Nine trace elements were determined in Withania
Somnifera. This important medicinal plant was found to be rich in Fe, Cu, Ni, Mn, and Zn. These trace elements are well known for curing diseases. The plant contains nutrient elements, which are best sources for fodder.

Mishra LC, Singh BB and Dagenais S. (2000) studied that the objective of this paper is to review the literature regarding Withania Somnifera (ashwagandha, WS) a commonly used herb in Ayurvedic medicine. Specifically, the literature was reviewed for articles pertaining to chemical properties, therapeutic benefits, and toxicity. Studies indicate Ashwagandha possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hemopoietic, and rejuvenating properties. It also appears to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems. The mechanisms of action for these properties are not fully understood. Toxicity studies reveal that Ashwagandha appears to be a safe compound. Preliminary studies have found various constituents of ashwagandha exhibit a variety of therapeutic effects with little or no associated toxicity. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using ashwagandha for a variety of conditions should also be conducted.

Kumar S. et al. (2010) studied that Withania Somnifera L. Dunal (Solanaceae), also known as 'ashwagandha' in Sanskrit and as 'Indian ginseng', is used widely in Ayurvedic medicine as a nerve tonic and memory enhancer, with antiaging, antistress, immunomodulatory and antioxidant properties. There is a paucity of data on the potential neuroprotective effects of W. Somnifera root, as traditionally used, against H(2)O(2)- and Aβ((1-42))-induced cytotoxicity which are current targets for novel approaches to treat dementia, especially dementia of the Alzheimer's type (AD). In this study, an aqueous extract prepared from the dried roots of W. Somnifera was assessed for potential protective effects against H(2)O(2)- and Aβ((1-42))-aggregated fibril cytotoxicity by an MTT assay using a differentiated rat pheochromocytoma PC12 cell line. The results suggest that pretreatments of differentiated PC12 cells with aqueous extracts of W. Somnifera root significantly protect differentiated PC12 cells against both H(2)O(2)- and Aβ((1-42))-induced cytotoxicity, in a concentration dependent manner. To investigate the compounds that could explain the observed effects, the W. somnifera extract was
analyzed by liquid chromatography-serial mass spectrometry and numerous withanolide derivatives, including withaferin A, were detected. These results demonstrate the neuroprotective properties of an aqueous extract of W. somnifera root and may provide some explanation for the putative ethno pharmacological uses of W. somnifera for cognitive and other neurodegenerative disorders that are associated with oxidative stress.

2.5.4.8 Azadirachta Indica (Neem):

Figure No: 23

Photo Courtesy: www.herbalextracts.in, Date: 30/10/2013, Time: 11:00 am

Joshi MC et al. (2003) studied that Propionibacterium acnes, an anaerobic pathogen, play an important role in the pathogenesis of acne by inducing certain inflammatory mediators. These mediators include reactive oxygen species (ROS) and pro-inflammatory cytokines. In the present study, ROS, interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were used as the major criteria for the evaluation of anti-inflammatory activity. To prove the anti-inflammatory effects of herbs, polymorphonuclear leukocytes (PMNL) and monocytes were treated with culture supernatant of P. acnes in the presence or absence of herbs. It was found that Rubia cordifolia, Curcuma longa, Hemidesmus indicus, and Azadirachta Indica caused a statistically significant suppression of ROS from PMNL. Sphaeranthus indicus caused a smaller, still significant suppression of ROS. Aloe vera had no effect on ROS production. In the case of proinflammatory
cytokine-induced monocytes, maximum suppression was shown by Azadirachta Indica and Sphaeranthus indicus, followed by Hemidesmus indicus, Rubia cordifolia, and Curcuma longa. Aloe vera showed insignificant inhibitory activity. Thus, these herbs show anti-inflammatory activity by suppressing the capacity of P. acnes-induced ROS and pro-inflammatory cytokines, the two important inflammatory mediators in acne pathogenesis.

Kumar M. (2006) studied that Methanolic of Musasapientum var. Paradisiaca (MSE, 100 mg/kg) was studied for its antiulcer and mucosal defensive factors in normal and non-insulin dependent diabetes mellitus (NIDDM) rats. NIDDM was induced by administering streptozotocin (STZ, 70 mg/kg, ip) to 5 days old rat pups. The animals showing blood glucose level > 140mg/dL after 12 weeks of STZ administration were considered as NIDDM positive. Effects of MSE were compared with known ulcer protective drug, sucralfate (SFT, 500 mg/kg) and anti-diabetic drug glibenclamide (GLC, 0.6 mg/kg) when administered orally, once daily for 6 days against gastric ulcers (GU) induced by cold-restraint stress (CRS) and ethanol and subsequent changes in gastric mucosal glycoproteins, cell proliferation, free radicals (lipid peroxidation and nitric oxide) and anti-oxidants enzymes (super oxide dismutase and catalase) and glutathione (GSH) levels. MSE showed better ulcer protective effect in NIDDM rats compared with SFT and GLC in CRS-induced GU. NIDDM caused a significant decrease in gastric mucosal glycoprotein level without having any effect on cell proliferation. However, all the test drugs reversed the decrease in glycoprotein level in NIDDM rats, but cell proliferation was enhanced in case of MSE alone. Both CRS or NIDDM as such enhanced gastric mucosal LPO, NO and SOD, but decreased CAT levels while CRS plus NIDDM rats caused further increase in LPO and NO level without causing any further changes in SOD and CAT level. MSE pretreatment showed reversal in the levels of all the above parameters better than GLC. Ethanol caused a decrease in glutathione level which was further reduced in NIDDM-ethanol rats. MSE reversed the above changes significantly in both normal as well as in NIDDM rats, while GLC reversed it only in NIDDM rats. However, SFT was ineffective in reversing the changes induced by CRS or ethanol or when given in NIDDM-CRS or NIDDM-ethanol rats. The results indicated
that the ulcer protective effect of MSE could be due to its predominant effect on mucosal glycoprotein, cell proliferation, free radicals and antioxidant systems.

Lahankar P. Magar S. and Dwivedi A. (2012) studied that ‘Mukhpak’ or ‘Sarvasar Rog’ is nothing but a recurrent mouth ulcer or Stomatitis and is also termed as Aphthous ulcer. Over consumption of extremely pungent and spicy food, consuming and chewing of chemical agents like Tobacco-Gutakha, Insomnia, Vitamin deficiency, many life threatening disease like Malignancy, Submucosal fibrosis, Skin disease and disturbances in G.I. tract like Constipation, Dysentery are the main causative factors responsible for this most common ENT ailment. In modern medicine, several mouth paints and mouth gargles are used for the treatment for Aphthous ulcer adjuvant to steroids, B’Complex group of drugs, injection placentrex (sub mucosal) which have their own limitations and there is no successful, satisfactory and cost effective treatment available. The trial preparation ‘Haridradi Tail’ i.e. medicated oil consisted of Haridra (Curcuma longa), Nimba patra (Azadirachta indica), Yastimadhu (Glycyrrhiza glabra), Neelkamal (Nelumbo nucifera) & Sesame oil (Sesamum indicum). This was clinically tried on 30 cases of mild to severe types of ‘Mukhapaka' in the form of 'Gandoosh', after every 4 hourly and also for oral administration, 10ml twice a day, for 10 days. It was observed that the trial preparation produces highly significant (p<0.05) symptomatic relief and causes marked improvement ulceration, present in buccal mucosal layer, burning sensation of palate, redness and erosion of oral cavity, difficulty in swallowing & chewing pungent things, enlargement of lymph nodes etc.

Arora D. et al. (2003) studied that the role of stress in the aetiology of several diseases is well recognized in Ayurvedic science and modern medicine. The stress is known as sahasa in Ayurveda. Sahasa by causing ojahksaya (loss of immunity) increases the susceptibility of the body to various diseases. Avoidance of stress is the best strategy for treatment and where it is not possible, the body should be well protected by taking appropriate care of the diet and sleep, sleep here indicates adequate rest required by the body. Further, regular intake of several rasayana herbs to increase the coping capacity of the body is advised. Several of these rasayanas have demonstrated significant stress
attenuating effects in animal experimentation and scientific efforts are ongoing to logically utilize rasayana herbal formulation in stress management.

Kadir M. Sayeed M. and Mia M. (2013) studied the Gastrointestinal diseases are common worldwide, including Bangladesh where majority of the rural people depend on water from unprotected sources. The people from Bangladesh use medicinal plants as their first line of health care to cure and prevent different types of gastrointestinal disorders. A total of 250 plant species of 93 families were listed. Leaves were the most cited plant part used against gastrointestinal disorders. Most of the reported species were tree in nature and decoction is the mode of preparation of major portions of the plant species. Most of the plant species were very common and were cultivated or planted in homestead or roadsides. The doses of the plants for different treatments varied widely. In view of the fact that the plants were selected based on their medicinal usage for treating different kinds of gastrointestinal diseases including diarrhea, the activities reported here need more works for validation and could be rationalized by the presence of active compounds found in those plants. The documentation represents the preliminary information in need of future phytochemical investigation and is important for the conservation of these plants.
Lee J. and Park W. (2011) studied that Myristicin (1-allyl-5-methoxy-3, 4-methylenedioxybenzene) is an active aromatic compound found in nutmeg (the seed of Myristica officinalis), carrot, basil, cinnamon, and parsley. Myristicin has been known to have anti-cholinergic, antibacterial, and hepatoprotective effects, however, the effects of myristicin on virus-stimulated macrophages are not fully reported. In this study, the anti-inflammatory effect of myristicin on double-stranded RNA (dsRNA)-stimulated macrophages was examined. Myristicin did not reduce the cell viability of RAW 264.7 mouse macrophages at concentrations of up to 50 µM. Myristicin significantly inhibited the production of calcium, nitric oxide (NO), interleukin (IL)-6, IL-10, interferon inducible protein-10, monocyte chemotactic protein (MCP)-1, MCP-3, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein (MIP)-1α, MIP-1β, and leukemia inhibitory factor in dsRNA [polyinosinic-polycytidylic acid]-induced RAW 264.7 cells \((P < 0.05)\). In conclusion, myristicin has anti-inflammatory properties related with its inhibition of NO, cytokines, chemokines, and growth factors in dsRNA-stimulated macrophages via the calcium pathway.
Kim H. et al. (2013) studied that Nutmeg (seed of Myristica Officinalis [MO]) is one of the most commonly used spices in the world and also a well-known herb for the treatment of various intestinal diseases, including colitis in traditional Korean medicine. The purpose of the current study was to investigate whether water extract of MF (MFE) can protect against dextran sulfate sodium (DSS) induced colitis in a mouse model. Colitis was induced by 5% DSS in balb/c mice. MFE (100, 300 or 1000 mg/kg) was orally administered to the mice twice a day for 7 days. Body weight, colon length, clinical score, and histological score were assessed to determine the effects on colitis. Proinflammatory cytokines (interferon-γ, tumor necrosis factor-α, interleukin [IL]-1β, and IL-6) were measured to investigate the mechanisms of action. MFE dose dependently inhibited the colon shortening and histological damage to the colon. However, it did not prevent weight loss. MFE also inhibited proinflammatory cytokines. The current results suggest that MFE ameliorates DSS-induced colitis in mice by inhibiting inflammatory cytokines. Further investigation, including the exact mechanisms is needed.

Yang W. et al. (2010) studied the exploring protective effects and mechanisms of Myristica officinalis Houtt Volatile oil on myocardial ischemic reperfusion injury in rat. Forty-eight wistar rats were randomly divided into six groups. After pretreatment 7 days respectively, beside blank group, the other groups was performed by liquating anterior interventricular branch of the left coronary artery of rat for 30min, then reperfusion by releasing the legating thread for 60min. Taking the tissue of myocardial ischemia and determining biochemical data of GOT, CK, LDH, MDA and SOD. Myristica officinalis houtt volatile oil could significantly decrease the content of MDA and the activity of CK, GOT and LDH and markedly increase the activity of SOD, and could degrade the incidence of heart rate. Myristica Officinalis Houtt Volatile oil has obviously protective effect on rat myocardial ischemic reperfusion injury.
Madisch A. et al. (2007) reported the objective of this study was to investigate the effect of Boswellia Serrata extract (BSE) on symptoms, quality of life, and histology in patients with collagenous colitis. Patients with chronic diarrhea and histologically proven collagenous colitis were randomized to receive either oral BSE 400 mg three times daily for 6 weeks or placebo. Complete colonoscopy and histology were performed before and after treatment. Clinical symptoms and quality of life were assessed by standardized questionnaires and SF-36. The primary endpoint was the percentage of patients with clinical remission after 6 weeks (stool frequency ≤3 soft/solid stools per day on average during the last week). Patients of the placebo group with persistent diarrhea received open-label BSE therapy for a further 6 weeks.

Kiela P. et al. (2004) studied that the extracts from Boswellia Serrata have been reported to have anti-inflammatory activity, primarily via boswellic acid-mediated inhibition of leukotriene synthesis. In three small clinical trials, boswellia was shown to improve symptoms of ulcerative colitis and Crohn's disease, and because of its alleged safety, boswellia was considered superior over mesalazine in terms of a benefit-risk evaluation. The goal of this study was to evaluate the effectiveness of boswellia extracts in controlled settings of dextran sulfate- or trinitrobenzene Sulfonic acid-induced colitis in mice. Our
results suggest that boswellia is ineffective in ameliorating colitis in these models. Moreover, individual boswellic acids were demonstrated to increase the basal and IL-1β-stimulated NF-κB activity in intestinal epithelial cells in vitro as well as reverse proliferative effects of IL-1β. We also observed hepatotoxic effect of boswellia with pronounced hepatomegaly and steatosis. Hepatotoxicity and increased lipid accumulation in response to boswellia were further confirmed in vitro in HepG2 cells with fluorescent Nile red binding/resazurin reduction assay and by confocal microscopy. Microarray analyses of hepatic gene expression demonstrated dysregulation of a number of genes, including a large group of lipid metabolism-related genes, and detoxifying enzymes, a response consistent with that to hepatotoxic xenobiotics. In summary, boswellia does not ameliorate symptoms of colitis in chemically induced murine models and, in higher doses, may become hepatotoxic. Potential implications of prolonged and uncontrolled intake of boswellia as an herbal supplement in inflammatory bowel disease and other inflammatory conditions should be considered in future clinical trials with this botanical.

Krieglstein C. et al. (2001) studied that the gum resin extract from Boswellia Serrata (H15), an herbal product, was recently shown to have positive therapeutic effects in inflammatory bowel disease (IBD). However, the mechanisms and constituents responsible for these effects are poorly understood. This study examined the effect of the Boswellia extract and its single constituent acetyl-11-keto-β-boswellic acid (AKBA) on leukocyte–endothelial cell interactions in an experimental model of IBD. Ileitis was induced by two subcutaneous injections of indomethacin (7.5 mg/kg) in Sprague-Dawley rats 24 h apart. Rats also received oral treatment with the Boswellia extract (H15) or AKBA at two different doses (low and high) equivalent to recommendations in human disease over 2 days. Controls received only the carriers NaHCO₃ (subcutaneously) and tylose (orally). Effects of treatment were assessed by intravital microscopy in ileal submucosal venules for changes in the number of rolling and adherent leukocytes and by macroscopic and histological scoring. Increased leukocyte–endothelial cell adhesive interactions and severe tissue injury accompanied indomethacin-induced ileitis. Treatment with the Boswellia extract or AKBA resulted in a dose-dependent decrease in rolling (up to 90%) and adherent (up to 98%) leukocytes. High-dose Boswellia extract as
well as both low- and high-dose AKBA significantly attenuated tissue injury scores. Oral therapy with the Boswellia extract or AKBA significantly reduces macroscopic and microcirculatory inflammatory features normally associated with indomethacin administration, indicating that the anti-inflammatory actions of the Boswellia extract in IBD may be due in part to boswellic acids such as AKBA.

Anthoni C. et al. (2006) studied the recent clinical trials of the gum resin of Boswellia Serrata have shown promising results in patients with ulcerative colitis. The objective of this study was to determine whether a semi synthetic form of acetyl-11-keto-β-boswellic acid (sAKBA), the most potent anti-inflammatory component of the resin, also confers protection in experimental murine colitis induced by dextran sodium sulfate (DSS) to compare its effects with those standard medications of ulcerative colitis like steroids and to examine whether leukocyte-endothelial cell adhesion is a major target of action of sAKBA. Clinical measurements of disease activity and histology were used to assess disease progression, and intravital microscopy was employed to monitor the adhesion of leukocytes and platelets in post capillary venules of the inflamed colon. sAKBA treatment significantly blunted disease activity as assessed both grossly and by histology. Similarly, the recruitment of adherent leukocytes and platelets into inflamed colonic venules was profoundly reduced in mice treated with sAKBA. Because previous studies in the DSS model have shown that P-selecting mediates these blood cell-endothelial cell interactions, the expression of P-selecting in the colonic microcirculation was monitored using the dual-radio labeled antibody technique. The treatment of established colitis with sAKBA largely prevented the P-selecting up regulation normally associated with DSS colitis. All of the protective responses observed with sAKBA were comparable to that realized in mice treated with a corticosteroid. Our findings demonstrated an anti-inflammatory effect of sAKBA and indicated that P-selecting-mediated recruitment of inflammatory cells is a major site of action for this novel anti-inflammatory agent.

Dr. Abdel-Tawab M. Werz O. and Schubert-Zsilavecz M. (2011) reported that Non-steroidal anti-inflammatory drug (NSAID) intake is associated with high prevalence of gastrointestinal or cardiovascular adverse effects. All efforts to develop NSAIDs that
spare the gastrointestinal tract and the cardio vasculature are still far from achieving a breakthrough. In the last two decades, preparations of the gum resin of Boswellia Serrata (a traditional ayurvedic medicine) and of other Boswellia species have experienced increasing popularity in Western countries. Animal studies and pilot clinical trials support the potential of B. Serrata gum resin extract (BSE) for the treatment of a variety of inflammatory diseases like inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and asthma. Moreover, in 2002 the European Medicines Agency classified BSE as an ‘orphan drug’ for the treatment of peritumoral brain edema. Compared to NSAIDs, it is expected that the administration of BSE is associated with better tolerability, which needs to be confirmed in further clinical trials. Until recently, the pharmacological effects of BSE were mainly attributed to suppression of leukotriene formation via inhibition of 5-lipoxygenase (5-LO) by two boswellic acids, 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA). These two boswellic acids have also been chosen in the monograph of Indian frankincense in European Pharmacopoeia 6.0 as markers to ensure the quality of the air-dried gum resin exudate of B. Serrata. Furthermore, several dietary supplements advertise the enriched content of KBA and AKBA. However, boswellic acids failed to inhibit leukotriene formation in human whole blood, and pharmacokinetic data revealed very low concentrations of AKBA and KBA in plasma, being far below the effective concentrations for bioactivity in vitro. Moreover, permeability studies suggest poor absorption of AKBA following oral administration. In view of these results, the previously assumed mode of action — that is, 5-LO inhibition — is questionable. On the other hand, 100-fold higher plasma concentrations have been determined for β-boswellic acid, which inhibits microsomal prostaglandin E synthase-1 and the serine protease cathepsin G. Thus, these two enzymes might be reasonable molecular targets related to the anti-inflammatory properties of BSE. In view of the results of clinical trials and the experimental data from in vitro studies of BSE, and the available pharmacokinetic and metabolic data on boswellic acids, this review presents different perspectives and gives a differentiated insight into the possible mechanisms of action of BSE in humans. It underlines BSE as a promising alternative to NSAIDs, which warrants investigation in further pharmacological studies and clinical trials.
2.6 Criticism of past Research.

1. Nazario B. (2011) describes that there are so many dietary treatments are available which can treat the Ulcerative Colitis but they have not specified the dietary treatment or any specific food which is more effective to cure the disease. It is necessary to give proper dietary treatment for ulcerative colitis patient so that the further research should be taken proper focus on the specific treatment.

2. Dr. Saibil Fred (2003) explained about the alternative treatments like homeopathy, Ayurveda and naturopathy. Also explained about the dietary modification and other therapies. They have considered all these treatments as a standard treatment options. But, as there are so many dietary treatments are available to cure the disease. So, the conclusion came out that rather than giving the other alternative therapies with medicines, the effect of such diets are more efficient to treat the diseases.

3. Belluzi A.et.al (2002) studied that in some of the ulcerative colitis patients the treatment of omega 3 fatty acid is useful but they have not mentioned the proper dosage of omega 3 fatty acid and the time limitations of it. It is necessary to mention the proper dosage of omega 3 fatty acid for the treatment of ulcerative colitis, so, that the time for taking the disease cured should be noted.

4. Kalk E. (2004) reported that the Probiotics drug used as a part of treatment for ulcerative colitis disease. But, as such there is no any specific dietary recommendation has been given related to Probiotics. It is necessary to inform about the dietary part and also the Probiotics can be used as a part of dietary treatment so, it should be also mentioned that the Probiotics rich diet can be given for the treatment of ulcerative colitis patients.

5. Zocco M.et.al (2006) evaluated that Aminosalicylates is a mainstay therapy for the treatment of ulcerative colitis. They said that Lactobacillus as a medicine works potentially on ulcerative colitis patients. As such they have not specifically mentioned for the use of Probiotics rich food groups.
2.7 Specialization of the Research

In the present study, the researcher has taken 3 experimental groups to see the effect of different type of dietary treatment groups. There are potentially the effect has been seen in the ulcerative colitis patient’s health that after the proper follow up of diet the symptoms of the disease has been gradually decreased. By every follow up the researcher came to know that the effect of L-Glutamine is prompt. After the 1\textsuperscript{st} effect, 2\textsuperscript{nd} effect came out from omega 3 fatty acid and the 3\textsuperscript{rd} effect came out from Probiotics dietary treatment group.

As there are so many researches has been done on this 3 elements. So, many researchers have suggested the elements for the treatment of ulcerative colitis. But, no one has compared these elements and sees the effect of these 3 elements together. As well as the Gastroenterologist are treating the patients of ulcerative colitis with allopathic medicines and treating the patients with Probiotics medicines. But, they don’t know the effect of these 3 elements which can really work as a part of dietary treatment on ulcerative colitis patients. So, being a dietitian this is the main key role to achieve the target to treat the patients of ulcerative colitis so, that patient may not depend on only medicines but patients can get easily cured with the proper treatment with diet also. It is also plays a major role for the treatment of ulcerative colitis disease.

In the present study, the researcher has taken these 3 elements in the dietary treatment group to see the specific effect of each element. This research can help out the doctors who are treating their ulcerative colitis patients. They will come to know about the specific dietary treatment with these 3 elements for ulcerative colitis patients and at last the patient can get fast and easily recovered from this disease.