International Journal of Herbal Medicine
Available online at www.florajournal.com

I J H M International Journal of Herbal Medicine

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2016; 4(3): 49-56
Received: 15-03-2016
Accepted: 17-04-2016

Dinesh Kumar
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

Mohini Sharma
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

Surender Verma
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

Kamal Saroha
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

Correspondence
Surender Verma
Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

Natural Polymers and Herbal Medicine Based Therapy for Colonic Diseases

Dinesh Kumar, Mohini Sharma and Surender Verma, Kamal Saroha

Abstract
Colonic drug delivery has gained remarkable importance for the delivery of the drugs for the treatment of local diseases associated with the colon. To achieve successful colonic delivery, colon targeting is of prime importance. Various natural therapies, available for the treatment of colonic diseases like ulcerative colitis, Intestinal bowel syndrome, colon cancer, diverticulitis, etc., are based on natural polymers such as guar gum, pectin, dextran, chitosan, inulin, amylose, etc. Interest in these biodegradable polymers is increasing day by day because these are safe, non-toxic, and economic and are chemically compatible with the other excipients in the formulation. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of human colon which make them potentially successful in targeted delivery systems to the colon. Some of the herbs used in the treatment of colonic diseases are *Aloe vera*, *Curcuma longa*, *Curcuma xanthorrhiza*, *Cynara scolymus*, *Ulmus rubra*, Psyllium, etc. There are certain preparations such as *Boswellia serrata* nanoparticles, curcumin microspheres available in the market to treat colon cancer. Recently, continuous efforts have been taken on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics. Hence, herbal medicine based treatment becomes widespread and prevalent, with encouraging results from clinical trials. Further evidence about the components of herbs and their bio-functions will shed light on clinical administrations of herb medicine in future. Keeping in view the safety of herbs, herbal medicine itself or in combination with conventional therapies would largely benefit patients with colonic diseases and other immune disorders.

Keywords: Colonic drug delivery, colonic diseases, natural polymers, herbs, approaches

1. Introduction
Colon is rich in lymphoid tissue and is the site where drug molecules which are poorly absorbed may achieve an improved bioavailability. It has less hostile environment with less intensity of activity than the stomach as well as small intestine. In addition, it has a longer retention time [1]. Colonic drug delivery is designed for local treatment of ulcerative colitis, irritable bowel syndrome (IBS), colon cancer, and diverticulitis [2]. In all these conditions, targeting of the active drug to the colon is important [3]. IBS is a functional gut disorder characterized by discomfort, bowel disturbances, blotting in a ratio 2:1 (women to men). The pathophysiology for IBS involves visceral hyper sensitivity, abnormal gut motility, intestinal micro biota, inflammation and immune disturbance, intestinal inflectional, etc. [4]. Ulcerative colitis and crohn's disease, are collectively known as Intestinal bowel disease (IBD). A combination of genetic susceptibility factors and mucosal immune system activation in response to luminal commensal bacterial antigens contributes to chronification of IBD [5]. Various natural polysaccharides have been used to deliver the drugs to colon [6]. These natural polysaccharides are degraded by the enzymes such as β-glucuronidase, β-xyloxidase, β-galactosidase, α-arabinosidase, nitroreductase, azoreductase, deaminase and urea hydroxylase, secreted by the bacteria such as bacteroids, bifidobacterium, eubacterium, peptococcus, lactobacillus, clostridium etc. present in colon [7]. Certain commonly used biodegradable polymers include guar gum, pectin, chitosan, xanthan gum, locust bean gum, karaya gum, starches, albizia gum, inulin, alginates, etc.[8]. Herbal extracts have drawn much consideration because of their multi-dimensional actions. Safe and effective drugs from herbal origin are available as compared to few options available through allopathic drugs [9].Various single herbal preparations available in the market are aloe Vera, curcuma species, Cynara scolymus, fumaria officinalis, hypericum perforatum, etc [4]. Certain formulations like *Boswellia serrata* as SLN [10], pectin-bora rice beads [1], curcumin microspheres to treat colon cancer, etc. are

available by using polymers [4]. Approaches to deliver intact molecule to the colon includes drug release based on variation of pH, gastrointestinal transit time, presence of colonic micro flora, pressure controlled drug delivery systems[6]. Various conventional pharmaceutical approaches for targeting drugs to the colon are pH sensitive system, microbial triggered systems- prodrug and polysaccharides based systems, time released systems [11].

2. Colonic diseases

Brief information about various colon diseases is as mentioned below:

2.1 Inflammatory bowel disease This disease is also known as IBD localized to specific sites in the gastrointestinal tract (GIT) and comprises of the following:

Ulcerative colitis

It is an inflammatory disease of large intestine characterized by motility and certain secretion disorders such as pus discharge, bleeding ulcer, diarrhea, acute flare-up, it is also known as colitis or proctitis[12]. It includes acute and chronic ulcerative inflammation of mucosa and sub mucosa of rectum and colon descending part. Sometimes, colon entire length is also involved [13].when defects occur in the protective barrier function of intestinal epithelium and the mucosal immune system, a dysregulated mucosal response takes place in the intestinal wall [14].

Crohn's disease

It is an idiopathic, chronic inflammatory disease known as regional enteritis. It involves discontinues distribution of lesions and may include any part of GIT from oral cavity to colon. It differs from ulcerative colitis since it causes deeper inflammation within the intestinal wall [12, 15].

2.2 Inflammatory bowel syndrome

It is defined as "abdominal pain or discomfort that occurs in association with altered bowel habits". Symptoms include abdominal pain, change in bowel habits (diarrhea or constipation), bloating and incomplete defecation. It is not present with gross organic or biochemical abnormalities. IBS can be classified as either diarrhea predominant, constipation predominant, mixed form [16]. The pathophysiology of IBS is multifactorial involving visceral hypersensitivity, abnormal gut motility, intestinal microbiota, inflammation and immune disturbance, abnormal gas handling, genetic factors and intestinal infections. It is a disorder that cannot be confirmed by a specific test and diagnosis is based on specific symptoms [17].

2.3 Colon cancer

It is also known as colorectal cancer or large bowel cancer which refers to cancerous growth in colon, rectum, or cecum. Colon cancer is attributable to diet. Risk factors related to colon cancer includes gender and ethnicity with a higher risk in male than the female and black than white respectively, old age, presence of adenomatus polyps, alcohol drinking and smoking habits, contraction of specific strains of human papilloma viral infections [18]. It is due to the accumulation of mutation in tumor suppressor genes and oncogenes [16]. Colorectal cancers arise from adenomatus polyps- clusters of abnormal cells in the glands covering the colon inner wall. These growths enlarge and then degenerate to become adenocarcinomas. It is a malignant epithelial tumor originating from glandular epithelium of the colorectal mucosa. Most colorectal cancer tumors are COX-2 positive. This enzyme is absent in healthy colon tissue but it is thought to be fuel abnormal cell growth. Staging of colon cancer is an estimate of the amount of penetration of a particular cancer. It is performed for research and diagnostic purposes and to determine the best method of treatment. Staging systems depends on the local invasion, degree of involvement of lymph node. Cancers that are confined within the wall of the colon (TNM stages 1 and 2) are curable with surgery. If untreated, they spread to regional lymph nodes (stage 3), where 73% are curable by surgery and chemotherapy [19].

3. Natural Polymers

Polymers are natural or synthetic high molecular weight macromolecules made up of repeated units of monomers. Polymers are generally used as pharmaceutical excipients. As biodegradability is an important factor in drug delivery systems, they are further classified as Biodegradable and non-biodegradable [20]. Polymers are used in the design of novel drug delivery systems that target the delivery of the drug to a specific region in the GIT or in response to external stimuli to the release of the drug. It can be carried out via different mechanisms like coating of tablets with polymers having pH dependent solubility [21]. Proteins, enzymes, muscle fibers, polysaccharides, gummy exudates are natural polymers mostly used in formulating various pharmaceutical products. Certain other natural polymers are chitosan, acacia, agar, gelatin, guar gum, shellac, etc. Polymers are monosaccharide's (sugars). Natural polysaccharides are used mainly for the development of solid dosage forms; these are highly stable, safe and nontoxic [22]. Polysaccharides are also known as Cinderella of biopolymers; they act like storage materials and are extracted as well as isolated from plant seeds [23].Various polysaccharides such as amylose, guar gum, pectin, chitosan, cyclodextrins, and locust bean gum, etc are used in colon targeted drug delivery systems [24]. Description of most commonly used polymers is as mentioned below:

3.1 Pectin

It is a non-starch linear polysaccharide that consists of α 1, 4 D-galactouronic acid and 1, 2 D-rhamnose with D-galactose and D-arabinose side chains having molecular weight between 50,000 to 1, 50,000. In comparison to other plant gums, pectin produces lower viscosities. Depending upon the plant source and preparation, it contains varying degrees of methyl ester substituents. Pectin is present in the walls that are surrounding the dividing and growing plant cells. In the junctional zone, it is present between the cells within secondary cell walls including xylem and fiber cells in woody tissue [21, 22]. The gelling property of pectin depends on degree of esterification and molecular size. Pectin can be chemically modified by saponification by acids, bases and enzymes [23]. It is completely degraded by colonic bacteria but is not digested in the upper GIT. Its solubility is its main disadvantage. Hence, to overcome this restriction, the degree of its methoxylation has been modified and calcium pectinate is prepared to make pectin resistant in the upper GIT [24].

A novel colon targeted tablet formulation using diltiazem hydrochloride and indomethacin as model drugs and pectin as a carrier was developed. In-vitro study reveals that from this dosage form, the release of drug is limited in stomach and small intestine and maximum release in colon. Thus, pectin can be used for targeting both water soluble and insoluble drugs. For fabrication of colonic delivery system calcium/ zinc

pectinate (lesser water soluble) is used. Dupuis *et al.* (2006) used zinc pectinate beads for colonic delivery of ketoprofen and reported similar performance when compared to calcium pectinate in hard capsules. The result obtained was that the zinc pectinate beads could protect the drug more efficiently from the upper GIT conditions and drug release will be controlled by pectin degradation with colonic micro flora [25].

3.2 Chitosan

It is a polycationic polysaccharide of high molecular weight derived from chitin by alkaline deacetylation [22]. Chitin is isolated from the exoskeleton of crustaceans such as crabs, krill. It is present in shell fish. It is a linear polymer of β (1-4) linked 2-amino-2-deoxy-D-glucopyranose. Its molecular weight is 1,43,000 to 2,10,000. Chitosan in dilute acetic acid in 1.25% concentration has very high viscosity, i.e., 120cps. It also contains 6.5% of nitrogen. It is a novel drug carrier material and is also used as a coating agent, gel former and to induce properties such as mucoadhesion and permeation enhancement to improve drug oral bioavailability [20]. Chitosan was used in oral drug formulations to provide colonic drug delivery. For colon targeting, it is considered as a promising candidate because of its properties like biocompatibility, non-toxicity and biodegradability [24]. It is used for colon targeted drug delivery, because of its tendency of getting dissolved in stomach acidic pH but get swollen in intestinal pH.

For colonic specific drug delivery, a chitosan dispersed system was prepared, which was composed of drug reservoir and an outer drug release regulating layer dispersing chitosan powder in hydrophobic polymer. The result was that the thickness of the outer layer controls the release rate of drug. An additional outer enteric coating was provided to prevent drug release from chitosan dispersed system in stomach because the dispersed chitosan dissolves easily under acidic conditions. By dissolving chitosan in various acidic conditions, different salts of chitosan were prepared followed by spray drying these solutions. The results were that the drug release reduced in acidic and alkaline pH when drug was mixed with chitosan salts [26].

3.3 Inulin

Inulin consist of β-(1-2) linked D-fructose molecules having a glucosyl unit at the reducing end. This polysaccharide gets degraded by colonic bacteria. It serves as a biodegradable compound with eudragit [24]. Inulin belongs to a class of fibers known as fructans. Some plants use it as a storing energy and are typically found in roots and rhizomes. The plants which synthesize inulin do not contain storing material starch. There are certain plants which contain high inulin content are dandelion (*Taraxacum officinale*), wild yam (Discora), onion (*Allium sativum*), and garlic (*Allium sativum*) etc. [23]. Inulin is incorporated into Eudragit RS films for the preparation of mixed films that resisted degradation in the upper gastrointestinal tract but digested in human fecal medium by the action of bacteroids [27]. Methylated inulin hydrogels were developed as colon specific drug delivery system, these hydrogels had large water uptake and anomalous dynamic swelling behavior. Inulin derivatised with succinic anhydride and meth acrylic anhydride produced a ph sensitive hydrogel that had a reduced swelling and low chemical degradation in acidic medium, but in the presence of inulinase (enzyme) has a good swelling and degradation in simulated intestinal fluid [21].

Preliminary studies have shown the synthesis and characterization of various hydrogels of inulin as carriers for colonic drug delivery system [27, 28]. Stubbe *et al.* (2001) developed azo containing polysaccharide gels such as azo dextran and azo inulin gels [29].

3.4 Guar gum

It is derived from the seeds of *Cyamopsis tetragonolobus*, having molecular weight of 1,000000. It is a galactomannan polysaccharide consisting of hydro colloidal polysaccharide of high molecular weight, composed of galactan and mannan units which are combined through glycosidic linkages. It is hydrophilic in nature and swells in cold water resulting in viscous colloidal dispersions. It is prepared by drying the pods in sunlight and then separating from the seeds. Commercially the gum is extracted from the seeds mechanically such as roasting, differential attrition, sieving and polishing. Its gelling property retards the release of the drug from the dosage form and also gets degraded in the colonic environment. By reacting guar gum with glutaraldehyde its swelling properties can be reduced. Guar gum is used as a carrier for indomethacin for colon specific drug delivery in ph 6.8 phosphate buffer saline containing rat caceal contents, using *in vitro* method studies. An attempt was also made to formulate oral controlled release zidovudine matrix tablets using guar gum as rate controlling polymer and to evaluate drug release parameters as per various drug release kinetic models; tablets were prepared by wet granulation method. Sustained release tablets of furosemide were prepared using guar gum, pectin and xanthan gum. The parameters evaluated were hardness, weight variation, friability and drug content. The result obtained was that the tablets with guar gum exhibited greater swelling index than those tablets with pectin and xanthan gum [30, 31].

3.5 Karaya gum

It is obtained from *Sterculia urens* (Family: Sterculiaceace). It is partially acetylated polymer of galactose, rhamnose and glucoronic acid. It is used as release controlling agent in producing directly compressed matrices, caffeine and diclofenac sodium were selected as model drugs [32]. It contains no starch and has lower water solubility but swells many times to its original volume. The powdered gum is used in lozenges, pastes and dental fixatives powders, also act as stimulant [20]. Studies have shown that mucoadhesive tablets prepared by karaya gum for buccal delivery, had adhesive properties superior than the guar gum and provided zero order drug release, but concentration greater than 50% w/w required to provide sustain release [32].

3.6 Xanthan gum

It is an extracellular polysaccharide of high molecular weight produced by the fermentation of the gram negative bacterium xanthomonas campestris. Due to the presence of glucoronic acid and pyruvic acid groups in the side chain has anionic character [8]. The primary structure of this contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D mannose-β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main

Chain. The non-terminal D-mannose unit in the side chain contains an acetyl function and the terminal D-mannose residue carry a pyruvate function [32]. It is also known as corn sugar gum, contains not less than 1.5% of pyruvic acid. It is soluble in hot and cold water and neutral to litmus, cream colored powder. The viscosity of 1% solution is about 1000cps [20].

Xanthan gum and hydroxypropylmethylcellulose were used as hydrophilic matrixing agent for preparing modified release tablets of diltiazem HCl. The tablets were prepared by direct

compression technique, the amount of both of these exhibited significant effects on drug release. As the result, xanthan gum showed higher ability to retard the release of the drug than synthetic hydroxypropylmethylcellulose [8].

3.7 Alginate

It is a natural polysaccharide polymer isolated from brown sea weed. Alginic acid is converted into its salt, of which sodium alginate form is mostly used. It is a linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in polymer chain [33-35]. Calcium alginate beads are prepared by drop wise addition of sodium alginate solution into calcium chloride solution. These beads are non-toxic and dried alginate beads can reswell in presence of dissolution media and can act as controlled release systems [31]. Calcium alginate beads were coated with Aquacoat® that is a pH-independent polymer followed by 2% w/w coating of Eudragit L-30D. Eudragit is an enteric polymer resist drug release in acidic media and triggered the release of drug at alkaline ph and controlled by thickness of Aquacoat®. When these beads loaded with drug swell to exceed the strength of outer sustained released coat, the film burst and drug gets released. This system delivers the drug to the distal intestine with minimum initial leak and provides sustain release in colon [8].

3.8 Starch

It is the principle form of carbohydrate reserve in green plants especially present in seeds and underground organs. A number of starches are recognized for pharmaceutical use such as maize (*Zea mays*), rice (*Oryza sativa)*, wheat (*Triticum aestivum*), and potato (S*olanum tuberosum)* [32]. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species [8]. It is composed of two polysaccharides, amylose and amylopectin. Amylose is a linear α-glucan containing α-(1, 4) bonds whereas amylopectin is more highly branched than amylose and contains 95% α-(1,4) and 5% α-(1,6) bonds. In starch, the amount of amylose present is between 20% and 35%. Starch resistant to digestive enzymes can be made by the formation of an amorphous structure (amylose amorphous) but can be degraded by colonic bacteria. Mostly, glassy amylose is chosen to provide colonic drug delivery. Due to the microstructure of amylose, it is used for colon specific formulations. Swelling in the aqueous media is one of the disadvantages of amylose in film form. In case of pure amylose films, upon exposure to aqueous media, considerable amount of water is taken up. They become permeable and before the distal GIT is reached the drug is already released in upper GIT [24].

Starch has also been evaluated for colon targeted delivery as enteric coated capsules. The resistant starch was studied for the improvement of gut micro flora and to improve clinical conditions such as IBS, immunostimulating activities and protection from colon cancer. The resistant starch was chemically modified by esterification, etherification or acidification. It may be acetylated, octenyl succinylated, carboxymethylated, hydroxypropylated and enzymatic or physical modification by crystallization was also done [27].

3.9 Chondroitin sulfate

It is a soluble mucopolysaccharide, belonging to a family of heteropolysaccharide called glycosaminoglycans (GAGs), found in humans cartilage, bone, cornea, skin, and arterial wall [23]. It is used as a substrate by bacteroids species in large intestine and is degraded by *B. ovatus* and *B. thetaiotaoimicron*. It consists of β-1, 3-D-glucuronic acid linked to N-acetyl-D-galactosamide. It is highly water soluble and thus, acts as a barrier in the colon targeted drug delivery formulations. Whereas, natural Chondroitin sulfate is readily water soluble and is cross linked but may not be able to sustain the drug release for most of the drugs from the matrix [26]. However, cross linked Chondroitin sulfate is less hydrophilic and thus can provide a better shield [27]. Rubinstein *et al.* (1992) developed colonic drug delivery systems based on cross linked Chondroitin sulfate and Chondroitin sulfate. The cross linking was done with 1, 12-diaminododecane. Cross linked Chondroitin sulfate, for indomethacin used as carrier, specifically for the large bowel [36].

Cavalcanti *et al.* (2005) characterized crosslinked chondroitin sulfate for specific drug delivery to colon Chondroitin sulfate was crosslinked with trisodium trimetaphosphate to reduce its hydrosolubility [37]. Amrutkar *et al.* (2009) prepared matrix tablet for colon specific delivery of indomethacin using chondroitin sulfate and chitosan as carrier and binder where Chondroitin sulfate was used to form polyelectrolyte complexes with chitosan, and its potential as a colon-targeted drug carrier was investigated. The study confirmed that selective delivery of drug to the colon can be achieved using cross-linked chitosan and chondroitin sulfate polysaccharides [38].

3.10 Cyclodextrins

These are cyclic oligosaccharides and consist of 6-8 glucose units linked through α-1, 4-glucosidic bonds. These are neither hydrolyzed nor absorbed from the stomach and small intestine [24]. In the colon, they undergo fermentation by the micro flora into small saccharides. This forms inclusion complex with drug molecules because interior of molecule is lipophilic while exterior is hydrophilic [27]. Minami *et al.* (1998) conjugated an anti-inflammatory drug with α, β and γ cyclodextrins primary hydroxyl groups through an ester or amide linkage. The in-vivo drug release behavior was investigated in rat. The results showed that in stomach and small intestine, these conjugates were found stable [39]. Thus, the cyclodextrins can be used for colon specific drug delivery and are also used to improve the drug properties such as solubility, stability and bioavailability [40].

4. Herbs used for treatment of colonic diseases

4.1 Ananus comosus

This belongs to. Bromelain, a mixture of proteolytic enzymes is derived from the stem of the pineapple plant *Ananus comosus* (family: Bromeliaceae). The major proteolytic component of Bromelain obtained from pineapple stem is stem Bromelain, with minor amount of fruit Bromelain, ananain and comosain. Oral treatment with Bromelain decreased spontaneous and piroxicam triggered colonic inflammation in IL-10-deficient mice *in-vivo*. In-vitro Bromelain treatment of colon biopsies from human IBD patients resulted in decreased secretion of proinflammatory cytokines and chemokines. Short term treatment with pineapple juice decreases colonic inflammation and long term treatment decreases chronic colonic inflammation [41].

4.2 Boswellia serrata

This herb belongs to the family Burseraceae and contains Boswellic acid and other pentacyclic triterpene acids. The major constituent is β-Boswellic acid [42, 43]. Positive effects of this herb reported are in some chronic inflammatory diseases including rheumatoid arthritis, bronchial asthma, osteoarthritis, ulcerative colitis and crohn's disease [44]. A pentacyclic

triterpenediol (TPD) was isolated from gum resin extracts of *Boswellia serrata*. TPD is a potential plant derived anti-cancer drug and is able to inhibit proliferation of large number of human cancer cell lines. In order to enhance its anticancer potential, it was formulated into SLN's by the microemulsuon method with 75% drug entrapment efficiency [10]. Despite the traditional claims, Boswellia extracts are ineffective in ameliorating colitis in dextran sodium sulphate induced colitis in mice. A clinical study was conducted on IBD patients, showed that; by inhibiting the activity and activated leucocytes adherence to intestinal mucosal cells, reduces the mucosal injury. A recent placebo controlled, double blind, randomized, parallel study in patients with crohn's disease showed no difference between the Boswellia treated and control group in disease remission [45].

4.3 Mentha piperita

The peppermint plant belongs to family Lamiaceae. In Ayurvedia, it is an important ingredient of formulations used in management if gastro-intestinal and skin disorders [46]. The constituents present are menthol, menthone, menthyl acetate, menthofurane, isomenthone, limonene, pulegone, and β-pinene [47]. With increased gas production, small intestine bacterial overgrowth and lactose intolerance are associated, which may sometimes trigger abdominal discomfort and bloating which are also the cardinal symptoms of IBS [48].

Steam distillation oil extracts from the peppermint plant are the oldest remedies for GI problems treatment. These extracts improve symptoms of IBS through spasmolytic effect on the smooth muscles in digestive tract. In a study, a group was provided with two enteric coated capsules containing 225 mg of peppermint oil twice daily. After four weeks of treatment, it showed a statistically significant improvement in overall IBS symptoms as compared to placebo group [16].

4.4 Curcuma longa

It belongs to the family zingiberaceae. It is a small perennial herb native to India bearing many rhizomes on its root system which are the source of its culinary spice known as turmeric and its medicinal extract called curcumin. Turmeric (*Curcuma longa*, zingiberaceae) is used for managing indigestion, abdominal bloating and abdominal pain. In 207 IBS patients, effectiveness of turmeric was investigated. Improvements based on symptoms and quality of life, were found after 8 weeks of turmeric intervention at a dose of 72 or 144 mg daily, in comparison to baseline and screening phases (but no placebo group). Since there were no differences between the two groups, indicates threshold effect or dose independent [16].

4.5 Cynara scolymus

The plant is known as artichoke belonging to the family asteraceae. Artichoke leaf extract is helpful for the patients with functional dyspepsia and may ameliorate symptoms of irritable bowel syndrome [49]. According to post marketing surveillance study of 279 subjects, two capsules of the extract three times daily with meals relieved cramps, bloating, abdominal pain, flatulence and constipation [16].

4.6 Tanacetum parthenium

The plant is known as feverfew, belonging to family Asteraceae. Because of its feathery leaves, it is also known as feather few. The name is derived from the Latin word "febrifugia" [50, 51]. The main active chemical in feverfew is parthenolide which plays an important role in treating cancer. A paper was published by Monica Guzman and her colleagues, in blood on the effect of parthenolide on chronic myologenous leukemia. The result obtained was that, it is the only chemical found which kills leukemia stem cells [52].

4.7 Fumaria officinalis

This herbaceous flowering plant, commonly known as drug fumitory or earth smoke, belongs to family Papaveraceae and contains fumaric acid as manin constituents. The plant also contains isoquinoline alkaloids like protopine and allocryptopine. Because of anti-spasmodic activity, it has been investigated in IBS patients. In the randomized, double blind, placebo-controlled trial. IBS related pain decreased more in fumitory group compared to the placebo group. IBS related distention increased in fumitory group and decreased in placebo group. However among the two different groups, changes in the IBS symptoms and psychological stress due to IBS do not differ significantly [53].

4.8 Zingiber officinale

It belongs to the family Zingiberaceae and consumed as a delicacy, medicine or spice. Traditionally, ginger is used to treat inflammatory gastrointestinal disorders. The ethanolic extract of dried rhizomes of ginger has showed protective effects against acetic acid induced UC in rats [44]. The effect of ginger on the initiation and post initiation stages of DMH induced colon carcinogenesis was studied in male wistar rats and resulted into lower incidence of tumors. Further, it was concluded by the researchers of same group that ginger supplementation suppressed colon carcinogenesis lipid peroxidation reduction and enhancing the enzymatic and non-enzymatic levels of antioxidants [19]. Ginger and its component zingerone were investigated to determine its anti-inflammatory activity in mice colitis induced by TNBS. They ameliorated TNBS-induced colonic injury in a dose-dependent manner. Their pathway investigation on gene expression profiles has been found to control cytokine-related pathways significantly. They suppressed TNBS-induced NF-κB activation and IL-1β protein level in the colon [54].

4.9 Glycyrrhiza glabra

Its common name is licorice and belongs to the family Fabaceae [44]. Licorice has also got immune modulatory and adaptogenic property, which is required for the pathogenesis of Ulcerative Colitis (UC). A number of active chemicals, including glycyrrhizin are thought to account for its biologic activity. Diammonium glycyrrhizinate is a substance that is extracted and purified from licorice, and may be useful in the treatment of UC [55]. Evidence has also reported that diammonium glycyrrhizinate could improve intestinal mucosal inflammation in rats and, importantly, reduce expression of NF-κB, TNF-α, and ICAM-1 in inflamed mucosa [56].

4.10 Triticum aestivum

Its common name is wheat and belongs to family Poaceae [44]. Wheat grass juice is used for treatment of various GI conditions. The amount of wheat grass used is 20ml/per day initially and can be increased to 100ml/day. No serious side effects are noticed and this juice appears to be effective and safe as an adjuvant or single treatment for active distal ulcerative colitis. A double blind study has demonstrated that supplementation with wheat grass juice for 1 month resulted in clinical improvement in 78% of people with ulcerative colitis, compared with 30% of those receiving a placebo [57].

4.11 Plantago ovata

Its common name is Isabgol and belongs to family Plantaginaceae [44]. Psyllium is used as dietary fiber, which is not absorbed by small intestine. Its mucilage absorbs excess water while stimulating normal bowel elimination. The mucilage obtained from Psyllium comes from seed coat. Plantago seed mucilage is often referred to as husk or Psyllium husk. Isabgol husk is a suitable carrier for the sustained release of drugs and is also used as a gastro retentive carrier. Psyllium seed husks are indigestible and are used to relieve constipation, IBS and diarrhea. Over the counter laxatives and fiber supplements such as Metamucil, colons cleanse, serutan, fybogel, bonvit, effersyllium and konsyl have Psyllium husks as their main ingredient [58].

The seeds of Isabgol ameliorated the development of colonic inflammation in transgenic rats as evidenced by an improvement of intestinal cytoarchitecture, significant decrease in some of the pro-inflammatory mediators and higher production of short chain fatty acids. In patients with ulcerative colitis; an open label, parallel group, multicentre, randomized clinical trial were conducted and revealed that Plantago ovata seeds (dietary fiber) might be as effective as mesalamine to maintain remission in ulcerative colitis [44].

4.12 Ulmus rubra

It is also known as slippery elm. The inner bark is dried and powdered and used for medicinal purposes. It is generally used for the treatment of sore throats, cough, gastroesophogeal reflux disease (GERD), ulcerative colitis, crohn's disease, irritable bowel syndrome, diarrhea, wounds, burns, boils, psoriasis. Slippery elm consist of a mucilage which gels on mixing with water thus coats and sooths the mouth, throat, stomach and intestines. Antioxidants are also present that relieve irritable bowel conditions. It also causes reflux stimulation of the nerve endings in the GIT leading to increased mucus secretion which protects GIT against ulcers and excess acidity [59, 60].

4.13 Dioscorea villosa

The herb belongs to the family Dioscoreaceae and the plant (wild yam) is also known as colic root. It also serves as an effective treatment for gall bladder inflammation, IBS and diverticulitis. Tincture of fresh root or trituration of resinoid dioscorein is used for acne, colic, constipation, cough, colds, flatulence, angina pectoris, renal colic, spinal irritations, pain in spleen [59]. Moalic *et al* 2011; carried out a study which provided evidence of regulation of cyclooxygenase expression and Nappez *et al* 1995; carried out a study and provided an evidence of lipoxygenase inhibition *in vitro* [60].

4.14 Hypericum perforatum

It is a yellow flowering, perennial herb also known as St John's Wort. It is beneficial in the management of IBS by modulating psychological stress and serotonin. During a 12 week randomized, double blind, placebo-controlled trial; the efficacy of *H. perforatum* was evaluated in IBS patients. The overall BSS (bowel symptom score) from base was decreased both in placebo and hypericum group, the placebo armed showed lower scores at the end of treatment. Another study revealed that *H. perforatum* can improve the ANS reactivity to stress and psychologic symptoms and relieve intestinal symptoms in women with IBS [4-61].

4.15 Paeonia lactiflora

It is a species of herbaceous perennial flowering plant belonging to family Paeoniaceae. The root of *P. lactiflora* is used in various herbal preparations of IBS. Paeoniflorin is the active ingredient. A dose dependent analgesic effect was produced by both intraperitoneal and central administration of Paeoniflorin on visceral pain in rats. The investigation further showed that this effect may be mediated by kappa-opioid receptors and α-adrenoreceptors in the CNS [62].

5. Conclusion

In the present paper, management of colonic diseases by herbal medicines has been evaluated in detail. Because of the relatively natural and multiple biological properties, herbs have emerged as the alternative for current treatment of colonic diseases like IBD, UC. Clinical trials have indicated the promising possibility of herb medicine for UC treatment. Meanwhile, herbal preparations are the mixture containing a huge range of biological compounds, other than purified single component. It might not be known which component in the herbs provides the exact pharmacological effects, even in some cases the herb mixtures exhibit clinical benefits. Thus, determination of herb components, dosage and course of herb treatment becomes a challenge for clinical employment. In addition, the safety of herb medicine remains to be further investigated, especially under long term treatment.

Hence, herbal medicine based treatment becomes widespread and prevalent, with encouraging results from clinical trials. Further evidence about the components of herbs and their bio-functions will shed light on clinical administrations of herb medicine in future. Keeping in view the safety of herbs, herbal medicine itself or in combination with conventional therapies would largely benefit patients with colonic diseases and other immune disorders.

6. Acknowledgement:

The authors express sincere gratitude to Prof. A.C. Rana, Director, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra for providing the library facilities.

7. References:

1. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. Journal of pharmacy and pharmaceutical sciences. 2003; 6 (1):33-66.
2. Ramteke KH Nath L. Formulation, evaluation and optimization of pectin-bora rice beads for colon targeted drug delivery systems. Advanced Pharmaceutical Bulletin. 2014; 4(2):167-177.
3. Madhavi M, Madhavi K, Jithan AV. Preparation and *in vitro*/ *in-vivo* characterization of curcumin microspheres intended to treat colon cancer. Journal of pharmacy and bioallied sciences. 2012; 4(2):164-171.
4. Roja A, Mohammad A. Herbal medicines for the management of irritable bowel syndrome: A comprehensive review. World Journal of Gastroenterology. 2012; 18(7): 589-600.
5. Liu zi, Yadav PK, Su JL, Wang JS, Fei K. Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease. World journal of gastroenterology. 2009; 15:5784-5788.
6. Rajguru VV, Gaikwad DP, Banker HV, Pawar PS. An overview on colonic drug delivery system. International Journal of Pharmaceutical Sciences Review and Research. 2011; 6(2):197-204.
7. Ravi V, Kumar Pramod TM. Siddaramaiah. Novel colon targeted drug delivery system using natural polymers. Indian journal of pharmaceutical sciences. 2008;

70(1):111-113.
8. Khandelwal M, Ahlawat A, Singh R. Polysaccharides and natural gums for colon drug delivery. The Pharma Innovation. 2012; 1(1):8-12.
9. Patel Biraju D, Patel Dhaval V, Chavada Jayant R, Dabhi Mahesh R, Manek Ravi A. Development and evaluation of pectin based colon targeted herbal drug delivery system. African Journal of Pharmacy and Pharmacology. 2012; 6(25):1815-1820
10. Bhushan S, Kakkar V, Pal HC, Guru SK, Kumar A, Mondhe DM, etc. Enhanced anticancer potential of encapsulated solid-lipid nanoparticles of TPD: A novel triterpenediol from Boswellia serrata. Molecular Pharmaceutics. 2013; 10:225-235.
11. Kothawade PD, Gangurde HH, Surawase RK, Wagh MA, Tamizharasi S. Conventional and novel approaches for colon specific drug delivery. E-Journal of Science and Technology. 2011; 2(6):33-56.
12. Verma S, Saini S, Kaul M, Rawat A. Colon: Diseases and approaches- An overview. International Journal of Pharmacy and Technology. 2011; 3(3):1197-1213.
13. Qureshi MA, Momin M, Rathod S, Dev A, Kute C. Colon targeted drug delivery system: A review on current approaches. Indian Journal of Pharmaceutical and Biological Research. 2013; 1(4):130-147.
14. Kotez U. Colon targeting of aminosalicylates for the treatment of ulcerative colitis. Digestive and liver disease. 2005; 37(6):381-388.
15. David Friend R. New oral delivery systems for treatment of inflammatory bowel disease. Advanced drug delivery reviews, 2005; 57:247-265.
16. Yoon SL, Grundmann O, Koepp L, Farrell L. Management of irritable bowel syndrome (IBS) in adults: conventional and complementary/ alternative approaches. Alternative medicine review. 2011; 16(2):134-151.
17. Vahedi H, Ansari R, Mir Nasseri MM, Jafari E. Irritable bowel syndrome: A review article. Middle East Journal of Digestive Diseases. 2010; 2(2):66-67.
18. Wong TW, Colombo G, Sonvico F. Pectin matrix as oral drug delivery vehicle for colon cancer treatment. AAPS Pharm SciTech. 2011; 12(1):201-214.
19. Sarkar P, Mahmud MAK. Gingerol might be a sword to defeat colon cancer. International Journal of Pharma and Biosciences. 2011;2(1):816-827
20. Kumar KK, Reddy BV. Biodegradable polymers and their role in drug delivery. PHARMATUTOR-ART-158.
21. Shanmugam S, Manavalan R, Venkappayya D, Sundaramoorthy K, Mounnissamy MV, Hemalatha S, *et al.* Natural polymers and their applications. Natural Product Radiance. 2005; 4(6):478-481.
22. Tiwari Akanksha, Kumar Raj Shukla. Natural polymer in colon targeting. International Journal of Pharmaceutical and Clinical Research. 2009; 1(2):43-46.
23. Reddy Kavitha, Mohan Krishna G, Satla Shobharani, Gaikwad Switi. Natural polysaccharides: versatile excipients for controlled drug delivery systems. Asian Journal of Pharmaceutical Sciences. 2011; 6(6):275-286.
24. Kushwaha Poonam. Natural polymers in colonic drug delivery. International Journal of Natural Product Science. 2014; 4(1):1-7.
25. Dupuis G, Chambin O, Genelot C, Champion D, Pourcelot Y. Colonic drug delivery: Influence of cross linking agent on pectin beads properties and role of capsule shell type, Drug Development and Industrial Pharmacy, 2006; 32:847-855.
26. Rajpurohit H, Sharma P, Sharma S, Bhandari A. Polymers for colon targeted drug delivery. Indian journal of pharmaceutical sciences. 2010; 72(6):689-696.
27. Vervoort L, van den Mooter G, Augustinjns P, Busson R, Toppet S, Kinget R. Inulin hydrogels as carriers for colonic drug targeting: I. Synthesis and characterization of methacrylated inulin and hydrogel formation. Pharm Res 1997; 14:1730.
28. Maris B, Verheyden L, Reeth KV, Samyn C, van den Mooter G, Augustinjns P, *et al.* Synthesis and characterisation of inulin-azo hydrogels designed for colon targeting. International Journal of Pharmaceutics. 2001; 213:143.
29. Stubbe B, Maris B, Vanden Mooter G, De Smedt SC, Demeester J. *et. al. In vitro* evaluation of azo containing polysaccharide gels for colon delivery. Journal of Controlled Release. 2001, 103-114.
30. Kumar R, Patil BM, Patil SR, Paschapur MS. Polysaccharides based colon specific drug delivery: A review. International Journal of Pharmtech Research. 2009; 1(2):334-346.
31. Prakash P, Porwal M, Saxena A. Role of natural polymers in sustained release drug delivery system: Applications and recent approaches. International Research Journal of Pharmacy. 2011; 2(9):6-11.
32. Shirwaikar A, Shirwaikar A, Prabu Lakshmana S, Kumar AG. Herbal excipients in novel drug delivery systems. Indian Journal of Pharmaceutical Sciences. 2008; 70(4):415-422.
33. Shun YL, Ayres JW. Calcium alginate beads as core carriers of 5-aminosalicylic acid. International Journal of Pharmaceutics. 1992; 212:19.
34. Lin SY, Ayres JW. Calcium Alginate Beads as Core Carriers of 5-AminosalicylicAcid. Pharmaceutical Research, 1992; 9:1128.
35. Kiyoung L, Kun N, Yueim K. Polysaccharides as a drug coating polymer. Polymer Preparations, 1999; 40: 359.
36. Rubinstein A, Nakar D, Sintov A. Chondroitin sulfate: A potential biodegradable carrier for colon-specific drug delivery. International Journal of Pharmaceutics. 1992; 84:141-50.
37. Amrutkar JR, Gattani SG. Chitosan-Chondroitin Sulfate Based Matrix Tablets for Colon Specific Delivery of Indomethacin. AAPS Pharm SciTech. 2009; 10:670-7.
38. Cavalcanti OA, Silva CC, Pineda EG, Hechenleitner AW. Synthesis and characterization of phosphated crosslinked chondroitin sulfate: Potencial ingredient for specific drug delivery. Acta Farmaceutica Bonaerense 2005; 24:234-8.
39. Minami K, Hirayama F, Uekama K. Colon-specific drug delivery based on a cyclodextrin prodrug: Release behavior of biphenylylacetic acid from its cyclodextrin conjugates in rat intestinal tracts after oral administration. Journal of Pharmaceutical Sciences. 1998; 87:715-20.
40. Wilson CG, Mukherji G, Sha HK. Modified-release Drug Delivery Technology. In: Rathbone MJ, Had graft J, Roberts MS, Lane ME, editors. Biopolymers and Colonic Delivery. 2nd ed. New York: Informa Healthcare; 2008; 1:295-309
41. Hale Laura P, Chichlowski Maciej, Trinh Chau T, Greer Paula K. Dietary supplementation with fresh pineapple juice decreases inflammation and colonic neoplasia in IL-10-deficient mice with colitis. Inflammatory Bowel Disease. 2010; 16(12):2012-2021.
42. Sharma ML, Khajuria A, Kaul A *et al.* Effects of salai

guggal ex-Boswellia serrata on cellular and humoral immune responses and leukocyte migration. Agent actions. 1988; 11:647-652.
43. Sharma ML, Bani S, Singh GB. Anti arthritic activity of Boswellic acids in bovine serum albumin (BSA) induced arthritis. International Journal of Immunopharmacology. 1989; 11:647-652.
44. Ammon HP. Modulation of the immune system by Boswellia serrata extracts and Boswellic acids. Phytomedicine 2010; 17(11):862-867.
45. Nahida T, Mariya H, Iqbal NH. Natural treatment for inflammatory bowel disease. Biotechnology, Bioinformatics and Bioengineering. 2014; 2(1):85-94.
46. Shah PP, Mello PMD. A review of medicinal uses and pharmacological effects of Mentha piperita. Natural Product Radiance. 2004; 3(4):214-221.
47. Chawla Snigdha, Thakur Monika. Overview of mint (mentha L) as a promising health promoting herb. International Journal of Periodontics and Restorative Dentistry. 2013; 5(6):73-80.
48. Alankar Shrivastava. A review on peppermint oil. Asian Journal of Pharmaceutical and Clinical Research. 2009; 2(2):27-33.
49. Bundy R, Walker AF, Middleton RW, Marakis G, Booth JC. Artichoke leaf extract reduces symptoms of irritable bowel sy ndrome and improves quality of life in otherwise healthy volunteers suffering from concomitant dyspepsia: a subset analysis. Journal of Alternative and Complimentary Medicine. 10(4):667-9.
50. Duke JA, Boca Raton. FL: CRC Press; CRC handbook of medicinal herbs. 1985.
51. Jackson B, McDonald RL. Magic and Medicine of Plants. In: Dobelis IN, editor. Pleasantville, NY: Reader's Digest Assoc; 1986.
52. Guzman ML, Rossi RM, Karnischky L, Li X. Peterson DR, Howard DS, Jordan CT. The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. Blood Journal. 2005; 105(11):4163-41639.
53. Brinkhaus B, Hentschel C, Von Keudell C, Schindler G, Lindner M, Stützer H, *et al*. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. Scandinavin Journal of Gastroenterology. 2005; 40:936-943.
54. Hsiang CY, Lo HY, Huang HC, Li CC, Wu SL, Ho TY. Ginger extract and zingerone ameliorated trinitrobenzene sulphonic acid-induced colitis in mice via modulation of nuclear factor-κB activity and interleukin-1β signalling pathway. Food Chemistry 2013: 136:170-177.
55. Kudo T, Okamura S, Zhang Y, Masuo T, Mori M. Topical application of glycyrrhizin preparation ameliorates experimentally induced colitis in rats. World Journal of Gastroenterology. 2011; 17:2223-8.
56. Yuan H, Ji WS, Wu KX, Jiao JX, Sun LH, Feng YT. Anti-inflammatory effects of *Diammonium Glycyrrhizinate* in a rat model of ulcerative colitis. World Journal of Gastroenterology. 2006; 12:4578-81.
57. Ben-Arye E, Goldin E, Wengrower D, Stamper A, Kohn R, Berry E. Wheat grass juice in the treatment of active distal ulcerative colitis: a randomized double-blind placebo-controlled trial. Scandinavin Journal of Gastroenterology. 2002; 37:444-9.
58. Fischer MH, Yu N, Gray GR, Ralph J, Anderson L, Marlett JA. The gel-forming polysaccharide of Psyllium husk (*Plantago ovata* Forsk). Carbohydrate Research 2004; 339(11):2009-17.
59. Langmead L, Dawson C, Hawkins C, Banna N, Loo S, Rampton DS. Antioxidant effects of herbal therapies used by patients with inflammatory bowel disease: An *in vitro* study. Alimentary Pharmacology and Therapeutics, 2002; 16:197-205.
60. Langmead L, Rampton DS. Review article: complementary and alternative therapies for inflammatory bowel disease. Alimentary Pharmacology and Therapeutics, 2006; 23:341-9.
61. Wan H, Chen Y. Effects of antidepressive treatment of Saint John's Wort extract related to autonomic nervous function in women with irritable bowel syndrome. International Journal of Psychiatry in Medicine. 2010; 40:45-56.
62. Zhang XJ, Li Z, Leung WM, Liu L, Xu HX, Bian ZX. The analgesic effect of paeoniflorin on neonatal maternal separation-induced visceral hyperalgesia in rats. Journal of Pain. 2008; 9:497-505.