Nat. Volatiles & Essent. Oils, 2021; 8(6): 4612-4624

NVEO
Natural Volatiles &
Essential Oils

A Review Of Inflammatory Bowel Disease Study On Zebra Fish And Its Herbal Cure

Lavanya S[1] , Gowri K[2,*] and Chitra V[3]

[1]Department of Pharmacology, Student, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District – 603203. India

[2]Department of Pharmacology, Associate Professor, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District – 603203. India

[3]Department of Pharmacology, Head of the Department, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District – 603203. India

Abstract

(IBD) Inflammatory bowel disease refers to a group of illnesses characterised by Prolonged inflammation of the gastrointestinal tract. IBD comprised of two kinds: (UC) ulcerative colitis and (CD) Crohn's disease. Both cause digestive problems and inflammation in the digestive system. Geographical location, incorrect nutrition, heredity, and an inappropriate immune response are the factors that influence IBD. It is more common in metropolitan areas than in rural areas, and it affects predominantly young individuals. Zebrafish larvae (Danio rerio) have proven to be an effective tool for studying IBD and gastrointestinal illnesses. The zebrafish's GI system is similar humans, that perform similar absorption and secretory functions. This review will provide some background information on the zebra fish investigation of inflammatory bowel disease, And Various environmental circumstances or exposures are connected to different genes.

Keywords: IBD, Zebra fish, Ulcerative colitis, Intestinal inflammation, Crohn’s disease.

Introduction

IBD (Inflammatory Bowel Disease) is a long-term, immunologically mediated gastrointestinal disease characterised by reversal and decline.[1] IBD is categorized into Crohn's disease and ulcerative colitis. The two major subtypes share a genetic susceptibility aetiology in which different genes are linked to various environmental events or exposures, as well as changes in the gut microbiota, all of which contribute to disease development.[2] IBD is characterised by a dysregulated immune response that causes and perpetuates intestinal inflammation and mucosal tissue destruction, as well as various intra and extraintestinal symptoms.[3] Diarrhoea and stomach pain are common symptoms of many chronic, relapsing, and remitting disorders. The large intestine and small intestine can create ulcers and scars in the intestines as a result of IBD. According to IBD research, patients with these illnesses have a weakened immune system. Genetic susceptibility and environmental conditions are among the other considerations.[4] Inflammatory bowel disease (IBD) is very common among white Europeans living in industrialised areas of the western globe. The reintroduced changes in environmental elements, such as contaminated foods, way of life factors, and medicine use, have contributed to changes in the disease's universality.[5] Although the proper pathophysiology of IBD is uncertain,[6] it is a decontrol hosts immunological reaction to the gut flora

in genetically sensitive humans.[7]The authors found the most convincing studies about the essential uses of natural products and plants in the treatment of IBD in this survey, which pose multiple cellular and molecular mechanisms that explain their anti-inflammatory and immune modulation action, side effects of novel drugs, and widespread use, some of which are life-threatening.[8] Ulcerative colitis is characterised by ulcers and inflammation of the colon lining. It nearly always affects the rectum, and bloody diarrhoea is the most common symptom.[9] Crohn's disease is an inflammatory condition that affects the gut wall's deeper layers. The disease can affect one or more segments of the small intestine (most commonly the ileum) or both the ileum and the colon (ileocolitis). Crohn's disease can also affect the intestines in certain people. Inflammation of the mouth, oesophagus, stomach, duodenum, appendix, or anus can occur.[10]

Epidemiology of IBD

Although the yearly occurrence of CD is currently significantly greater in the northern part of America, with 20.3 per 100,000 per individual –years, the annual occurrence of ulcerative colitis is raised in European countries, with 24.3 per 100,000 per person per year.[11] Both UC and CD have the highest prevalence in Europe, with 505 and 349 cases per 100,000 people per year, respectively.[12] However, IBD appears to be more prevalent in countries such as France and Scotland. For example, the prevalence of IBD is increasing in countries such as New Zealand and Australia. Cases of IBD are on the rise in other low-affected regions, such as Asia and other developing countries.[13] As the prevalence of IBD has increased, As IBD has risen in developing countries, UC cases numbers are higher, followed by a growing incidence of CD currently such scenario is being widely noticed in various parts of Asia.[14]These above data strongly backups the argument that environmental factors and lifestyle are the main co factors in the cause of IBD.[15] Importantly, there are only confined and private study data on the epidemiology of IBD to date in underdeveloped countries .More precise means of evaluating.[16]

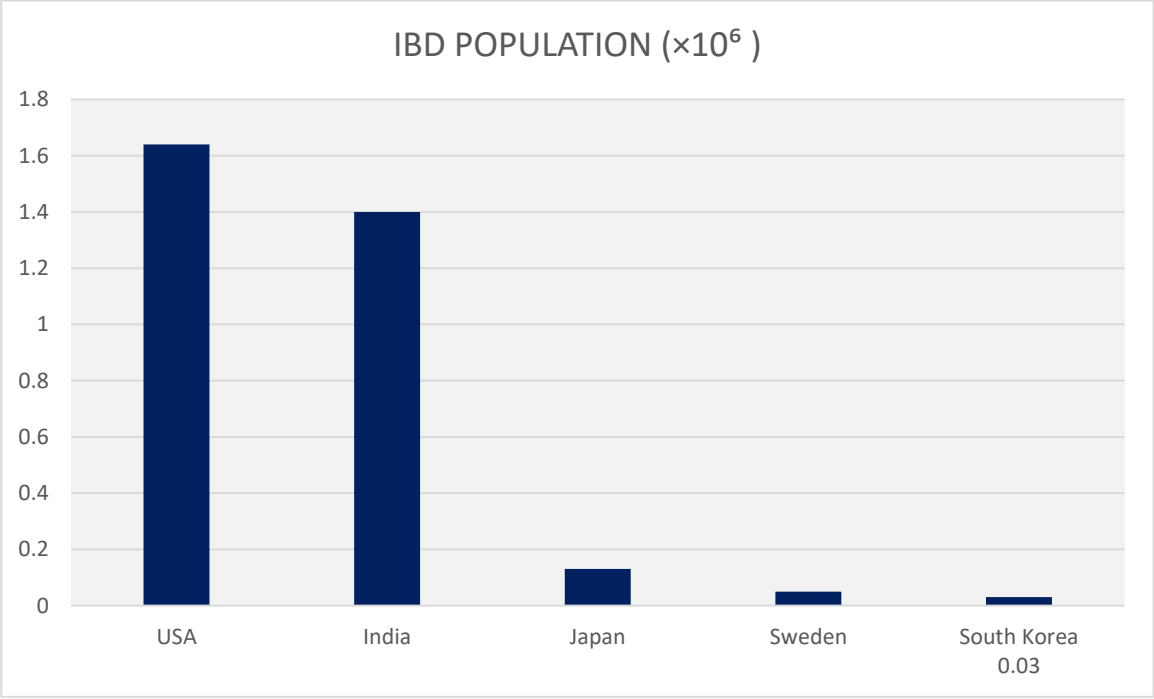

FIG: 1 IBD Epidemiology

Pathogenesis

Causes and Risk factors:

The precise causes of ulcerative colitis are unknown. Finally, scientists believe that there is a single cause in which many factors interact to cause the illness. Furthermore, the cause of one individual's illness may be completely different from that of another.

Genetics

There have been numerous advances in our understanding of genetic contributions to IBD. The gene loci associated with IBD are said to be 163, of which 110 were recently linked with both diseases, 30 CD precise and 23 UC specific.[17] Studies of gene loci shared by CD and UC may provide a more accurate method of determining their common pathogenesis.[18] The first vulnerability gene for CD was discovered in 2001, with the discovery of NOD 2, which stands for Nucleotide-binding oligomerization Domain containing 2 Autophagy, which is induced by MPD stimulation, regulates bacterial replication and antigen presentation.[19]

Environment

Whereas the risk of CD was increased, in contrast to the outcome of UC, resulting in a higher percentage of post-operative disease, there has been a greater recognition of vitamin-immunologic D's role.[20] Genetics, and thus the system response, may not be sufficient to explain the occurrence of inflammatory bowel disease. There are also one or more conditions that can cause IBD, which include the following.

Air pollution

IBD arose as a result of industrialization. Air pollution has risen tremendously, especially in emerging nations, which are experiencing rapid evolution at the same time as experiencing the greatest increase in IBD incidence.[21] The gut can only be affliated to inhalation of toxic gases, mucocilliary consent of particulate matter (PM) from the airways, and contaminating of foodstuffs and beverage goods.[22]

NSAIDS

As it has been related to ulcerative colitis flare-ups, this type of pain medicine is normally used with precaution in persons with ulcerative colitis. NSAIDs have the risk to disrupt the canal also in those who do not have IBD. The internal organ mucous membranes of the abdomen, tiny viscus, and colon will be harmed by NSAIDs. NSAIDs may cause internal organ porosity by inhibiting COX, which decreases autocoid production.[2324] Prostaglandin inhibition has been studied in IBD because of its immunoregulatory effects, most notably the inhibition of growth mortification and the induction of medication cytokines such as lymphokine (IL).COX-1 and COX-2 are two types of the crucial enzyme cyclooxygenase (COX).[25] COX-1 is found in high concentrations in several human tissues. In contrast, COX-2 is an inactivating enzyme that is triggered by inflammation.[26]

Antibiotics

In a few cases, antibiotics have been observed to induce flare-ups of the condition. Antibiotics have been related to an increased risk of developing a kind of IBD in some studies, particularly when administered for a long length of time or in children.[27]

Smoking

Ulcerative colitis is also known as "non-smoker's illness." People who have quit smoking find the sickness even more. It is not recommended that those who have been diagnosed with inflammatory bowel disease cease or return to smoking. Smoking's detrimental effects on the body far outweigh any potential benefits for inflammatory bowel disease.[28]

Liquor

Several studies have proven that alcohol consumption has a protective effect on UC advancement. Regardless, when drinking alcohol is combined with smoking,[29] this outline is null and void. There were no significant differences in CD progression between people who consumed alcohol at least four times per week and teetotallers.[30]

Nutrients and Minerals

Many research have looked at the long-term consequences of eating a lot of monosaccharides on IBD improvement.[31] emphasised the impact of excessive cola-type beverages and candy on increasing IBD occurrence.[32] confirmed their perception, stating that desserts and fake sugars have an unmistakable negative impact on the ability to build up each UC and CD. In any case, in 2014,[33]reported the findings of a large-scale planned study of over 400000 men and young ladies, concluding that there is no link between total carbohydrate, sugar, or starch consumption and the rate of UC. It should be noted that consuming milk sugar does not increase the risk of IBD.[34] A high protein and fat consumption may increase the risk of IBD progression.[34] Similar researchers agree that a high fat diet, particularly one high in cholesterine, may increase the incidence of IBD.[35] confirmed the result associate high consumption of linolic corrosive, on the possibility of UC advancement had been further more incontestable. This carboxylic corrosive could be a precursor to arachidonic corrosive, which has pro-inflammatory metabolites.[36] The use of this can also increase the risk of UC, whereas an increase in monosaturated carboxylic acid may be a preventive measure.[37] In people with inflammatory bowel illness, vitamin D insufficiency may be a prevalent improvement. Few studies see this deficiency as a delivery issue that will increase the risk of IBD development.[3438] One study found that weight control plans based on liquids, Mg, and ascorbic acid reduced the risk of IBD development, while another study found that retinol-rich foods increased the risk of IBD development.[3439] It should be noted that the use of leafy foods juices, because of the fibre and ascorbic corrosive substance, may speak to a different natural procedure issue that decreases the risk of developing IBD because of their anti-oxidative activity.[40]

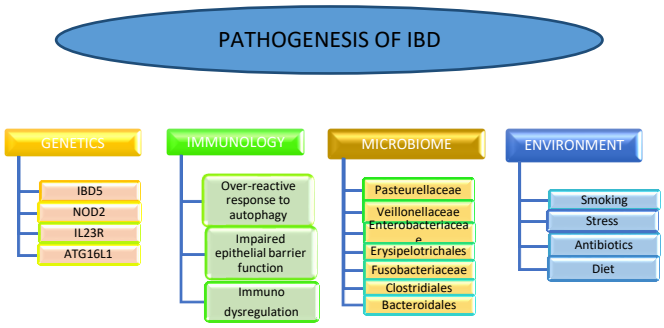

Fig. 2: Inflammatory Bowel Disease Pathogenesis

Zebra fish model in IBD

Zebrafish larvae (Danio rerio) have been shown to be an useful tool for investigating IBD and gastrointestinal diseases.[41] The zebrafish's GI system is very similar to humans, with a similar internal organs that perform indistinguishable absorptive and secretion mechanism. A genomic sequencing revealed over 70% of human genes had zebrafish sequences.[42] This highest percent of similarity, combined with a better understanding of the relevant genetic features, may aid in the finding of IBD genetic variants.[43] NOD1 and NOD2 are two types of nucleotide binding oligomerization domain which have

proteins that identify bacterial substances and initiate an immune response.[44] As a result, zebrafish could be employed as a tool in investigations of the genomic and ecological factors that contribute to IBD etiology. Zebrafish have already aroused the interest of researchers due to their susceptibility to mutagenesis and the availability of genetic technologies.[45] The three primary types of strains employed in zebrafish models for IBD research are transgenic strain, mutant strain, and wild-type strain.

Gross Anatomy

The intestine of an adult zebrafish is a folded tube that takes up the majority of the abdominal cavity. Zebrafish, like other cyprinids, have no stomach. The anterior intestine, also known as the intestinal bulb, has a larger calibre than the posterior intestine's lumen and hence may serve as a reservoir. The existence of huge randomly formed epithelial folds can be seen when the intestinal wall is illuminated, which is transparent. These folds are substantially greater in proportion to the finger-like intestinal villi found in mammals and other amniotes. Although many folds are orientated circumferentially, a considerable number of folds are arranged arbitrarily. The mid intestine has a smaller fold height than the anterior intestine. The posterior intestine segment is defined by the shortest longitudinally oriented folds.[46]

Breeding and Cultivation

Comparing to Mice model, Zebrafish are less difficult to raise. Zebrafish are extremely fertile. Over the course of 3–4 months, each female lays hundreds of egg, which could be fertilised In vitro. The zebrafish model are constructed more quickly than the mice model. It works best for research that require a large number of sample data points. Furthermore, the embryos' optical transparency and quick development enable for monitoring, manipulation, and drug screening.[47]

Advantages of Zebra fish models

Researchers have been using IBD animal models for almost a century, from drug-induced models to transgenic models. Despite the fact that numerous models are human-like, none exactly mimic the pathophysiology of IBD. Inflammation of intestine can occur naturally in some animals, which are known as spontaneous IBD models. Cotton-top tamarin (CTT) displays pathological changes similar to UC and a poor health of colon, adenocarcinoma in adult CTTs, making it an appealing model for Ulcerative Colitis associated colon cancer.[48] IBD research utilising zebrafish models has recently focused on five areas: genetics, growth, endoplasmic reticulum (ER) and gut microbial immune interactions.

Induction of intestinal inflammation in Zebrafish

IBD is the inflammatory disorder in which the digestive tract becomes irritated. It is induced in zebrafish on treating them with chemicals like DSS, TNBS, Oxazolone etc.,[49] Oxazolone produce IBD in Adult Zebrafish when given intrarectally which is characterised by granulocyte infiltration, epithelial degradation, and elevated expression of cytokine (tnf-alpha, interleukin-1b, interleukin-10).[50] TNBS is also produce IBD in zebrafish when given intrarectally which cause elevated level of intestinal mRNA and melanin concentrating hormone.[51] Variation of TNBS Concentration found no alterations in intestinal cell shape.[52] Exposure of zebrafish in the mixture of egg, TNBS, and water elicited an inflammatory reaction in the stomach between 3 and 8 dpf.[53] The intestinal structure and movement of zebrafish could be examined by giving a fluorescent dye that which revealing TNBS-induced intestinal dilation, villus length reduction, crypt expansion, and peristalsis loss. Histopathological examination revealed the length of the gut, an enlargement of the lumen, an increase in the number of goblet cells, villi and clefts.[53] TNBS therapy increases neutrophils count in gut, and the cytokine expression are ccl20, tnfa,mmp9, interleukin-1B and interleukin-8.[54] Dextran sodium sulphate (DSS), a detergent, has also been used to promote intestinal inflammation in zebrafish larvae. DSS mimics multiple features of TNBS-induced IBD, including enhanced

pro-inflammatory genetic expression and neutrophil number in the colon. The inflammatory pattern of DSS induced IBD was not similar to TNBS induced IBD.[55] Glafenine (NSAID), is also used to produce IBD in zebrafish, leads to severe gut abnormalities after 12 hours of treatment. Glafenine was found to trigger apoptosis and shedding in intestinal epithelial cells due to unfolded protein response and ER stress.[56] Glafenine sheds epithelial cells in gut by inhibiting multidrug resistance (MDR) efflux pumps. This shedding protects the organism by reducing inflammation and increasing survival.[57] Furthermore, soybean meal is used as a fish feed which promote inflammation of intestine in zebrafish. This inflammation has been related to soy saponin rather than soy protein, and is characterised by migration of neutrophil to gut and transcription levels of cytokines (il1b and il8) are elevated[58] Soybean saponins and protein isolates, which is stained with Sudan black were observed to enhance the amount of neutrophils in the gut, and also the gene expression associated to the non specific immune system (interleukin-1b, tnfa, c3b, saa, mpx) in a later investigation.[59] Inflammation cause rise in GI permeability, reduce absorption of protein, and change the constitution of gut flora.[60] Th17 (T helper cell) is required for soybean meal-induced intestinal inflammation.[61] When looking at the long-term impacts, it was discovered that beginning stage of soy protein or soybean meal feed had programming effects on inflammation in juveniles.[62] Because soybean meal is a common commercial fish food, researchers have looked for ways to mitigate its pro-inflammatory effects. And the typical cholinesterase inhibitors have all been found to block soybean meal induced IBD including microalgae,[63] lactoferrin,[64] aloe vera,[65] galantamine,[66] and a Bacillus subtilis strain that produces phytase. [6759] In zebrafish, the varied composition of the gut microbiota has been demonstrated to be a key determinant of intestinal inflammation.[60] Adult zebrafish treated with vancomycin or colistin sulphate had varied intestinal microbiota components, which impacted the severity of the oxazolone-induced enterocolitis and the makeup of the intestinal leukocyte infiltrate.[52] Treatment of Zebrafish larvae with the broad-spectrum antibiotics kanamycin and ampicillin reduced death rate after TNBS exposure while also preventing the development of pro-inflammatory expression of genes and leukocyte transit to the colon, resulting in a considerable loss of microbiota.[54] TNBS induced IBD produces histological alterations in the gut, and also increases the pro inflammatory cytokines, was completely dependent on the existence of local microbiota, using a technology to manufacture sterile zebrafish larvae.[68] In TNBS induced colitis, the proportion of Proteobacteria is increased in the microbiota while the quantity of Firmicutes decreased, and these changes were linked to the severity of the enterocolitis.[69] Cotreatment with Anisakis (nematode) reduces mortality and pro-inflammatory gene expression in adult zebrafish. Parasitic helminths effects may protect against IBD.[70] Anti-inflammatory and antibacterial medications increased the response to TNBS were used to further investigate the validity of the TNBS-induced IBD model in larvae.[5354] This model was also used to screen a small number of drugs, including NOS inhibitors, thalidomide, and parthenolide. NOS inhibitors were able to restore the disease phenotype in vivo, as assessed by histological testing, while thalidomide and parthenolide reduced TNF expression (based on immunohistochemistry).[53] TNBS-induced intestinal expansion and neutrophils infiltration were also reduced by Thermus thermophilus HB27 hyperthermostable superoxide dismutase.[7172] In the DSS-induced animal, the importance of retinoic acid in reducing pathogenic intestinal mucus production was also demonstrated.[55] Furthermore, prostaglandin E2 was found to be capable of rescuing the damage of gastric mucosal layer and epithelial barrier destruction caused by DSS, thereby providing damage prevention. Mesalamine and 6-mercaptopurine, commonly used IBD medications which showed injury protection in the DSS model.[72]

Herbal treatment for IBD

Herbal therapy is the oldest kind of healthcare, and herbal medicines have been used by all countries throughout history. Many herbal remedies have immunomodulatory properties. As a result, it appears acceptable to test herbal treatments in IBD patients. Good, extensive clinical trials assessing the efficacy of

herbal therapy in IBD. Herbal treatments for IBD work through a variety of mechanisms, which are discussed below. In IBD, alteration in Dendritic cells, Natural killer cells, macrophages and neutrophils are occurs. TNF production alters epithelial permeation and Ionic transport resulting in lesion and mucosal inflammation.[73] Aloe vera gel shows antibacterial and anti-inflammatory responses. Aloe vera gel can block the secretion of IL8 and prostaglandin. Boswellia herb is mainly used to treat Ulcerative colitis. Boswellic acid from the Boswellia herb inhibits 5-lipoxygenase, which is a major component of the inflammatory process in IBD. This finding supports the use of Boswellia for treating UC. Furthermore, it reduces Gut motility directly through L-type Ca2+ channels. In rodents, boswellia herb preventing edoema and inflammation in the intestine caused by chemicals. According to other research, it has cytotoxic characteristics.[74] The powdered bark of the slippery elm tree is used to make a supplement called slippery elm. Native Americans have traditionally used it to cure coughs, diarrhoea, and other gastrointestinal issues. Slick elm has recently being investigated as a supplement for IBD.[75] When utilised in people with IBD, a study found that slippery elm had antioxidant properties.[76] Bromelain is used to treat inflammation such as sinusitis, arthritis. Investigations shows Bromelain is a potential supplement for IBD, particularly in UC. Bromelain, is the active component of pineapple, may help alleviate the inflammation. Bromelain's anti-inflammatory action on T-cell activation and cytokine release requires proteolytic activity.[7778] Bromelain inhibits the cell surface receptors such the hyaluronan receptor (linked to leukocyte migration and the production of pro-inflammatory mediators).[7980] Garlic (Allium sativum) possesses antibacterial characteristics that can aid in the reduction of microbial content and so relieve IBD symptoms.[81] Curcumin prevents NF-B from becoming activated. Many antioxidant enzymes are synthesised with the help of NF-B. It binds with thioredoxin reductase and transforms its antioxidant activity to severe pro oxidant in an irreversible manner. Liquorice is also used to treat inflammatory bowel disease (IBD). In addition, studies suggest that diammonium glycyrrhizinate can lower the expression of cytokines such as TNF-, ICAM-1, and NF-B. The NF-B proteins are eukaryotic transcription factors that regulate inflammation and inflammatory responses. NF-B is elevated on IBD[8283] Camellia sinensis and Commiphora inhibits IKK and NF-B. NF-B Kinase (IKK) activates the transcriptional factor NF-B.[84] As a result, IKK and NF-B suppressors can be utilised to treat IBD. Tormentil extract is supplemental treatment for Prolonged inflammation of intestine of their antioxidative characteristics. Guggul plant contains guggulsterone (steroid) has a anti-inflammatory property capable of preventing and treating T-cell–induced colitis. Guggulsterone dramatically decreased the disease activity index, Length of the colon, and mucosal in DSS treated mice. And guggulsterone reduces upregulation of IB and IKK phosphorylation in DSS treated mice.[85] Nicotine obtained from Nicotiana tobacum was reported to reduce LTB4 levels in TNBS induced colitis.[86] Nitric oxide levels and the inducible isoform of Nitric oxide synthase are elevated in IBD.[87] Some herbal therapies, such as Gardenia jasminoides glycoprotein,[88] Polygonum multiflorum -glycoside,[89] Clonorchis sinensis-theaflavin-3,3'-digallate[90] are beneficial against IBD by reducing Nitric oxide and isoform of Nitric oxide levels. Cox-1 and Cox-2 are cyclooxygenase isoforms that catalyse the synthesis of prostaglandins. Prostaglandins produced by Cox-1 are essential for maintaining stomach cytoprotection and blood flow and Prostaglandins, which are generated by Cox-2, help to control inflammation.[91] Some studies reported that Gardenia jasminoides and Curcumin reduces Cox-2 levels.[92] Platelet numbers have elevated in patients with IBD exacerbations[93] Herbal antiplatelet drugs like Angelica sinensis reduces activation of platelet, reduce endothelial cell damage, and improve microtransmission in patients with IBD.[94]

CONCLUSION:

Inflammatory bowel disease is a long-term immunological illness of intestine. It is comprised of two conditions (Crohn's disease and Ulcerative colitis). IBD results from unregulated local immune response to normal commensal microbes in the gut. Crohn disease has driven by Th1 response, Ulcerative colitis has

driven by Th2 response. Th17 is also involved in the gut inflammatory response in IBD. NOD2 mutation, connected with highest risk of Crohn's disease whereas NOD1 is associated with Ulcerative colitis. Environmental variables including as smoking, stress, vitamin D deficiency, NSAIDs, antibiotics, and liquor increase the risk of IBD. Zebrafish larvae (Danio rerio) have been demonstrated to be an effective tool for studying IBD and gastrointestinal illnesses. GI tract of the zebrafish is very similar to humans, with all internal organ, performing same absorption and secretion activities. Because of their genetic and immunological similarities with humans, Now a days zebrafish are replaced by mice model. Using freshly developed strains and high-throughput genetic and Biochemical screening, researchers can detect the suppressors and promoters of inflammation. Zebrafish models are used to assess whether the output of IBD susceptibility genes are hazardous. Despite the fact that chemically produced models induce inflammation, they do not meet the criteria for IBD. The zebrafish is a economical laboratory animal which having numerous applications. Herbal therapy is the oldest form of healing, and it has been used by all countries. Immunomodulatory characteristics are seen in several herbal medicines. As a consequence, it indicates that testing herbal remedies in IBD patients is acceptable. Herbal therapy is both safe and effective in the treatment of IBD.

CONFLICT OF INTEREST:

The authors have no conflicts of interest

ACKNOWLEDGEMENTS:

We thank Dr. V.chitra, Dean, SRM college of Pharmacy, SRM Institute of Science and Technology and also the staffs of Department of pharmacology, SRM College of pharmacy, SRMIST for the encouragement and support.

REFERENCES

Salminen, S. et al. Functional food science and gastrointestinal physiology and function. Br. J. Nutr. 80, S147–S171 (1998).

Gray, W. N., Denson, L. A., Baldassano, R. N. & Hommel, K. A. Treatment Adherence in Adolescents With Inflammatory Bowel Disease: The Collective Impact of Barriers to Adherence and Anxiety/Depressive Symptoms. J. Pediatr. Psychol. 37, 282–291 (2012).

De Ponti, F. & Tonini, M. Irritable Bowel Syndrome. Drugs 61, 317–332 (2001).

Kandhare, A. D. et al. Effect of hydroalcoholic extract of Hibiscus rosa sinensis Linn. leaves in experimental colitis in rats. Asian Pac. J. Trop. Biomed. 2, 337–344 (2012).

Abegunde, A. T., Muhammad, B. H., Bhatti, O. & Ali, T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. World J. Gastroenterol. 22, 6296 (2016).

Podolsky, D. K. The current future understanding of inflammatory bowel disease. Best Pract. Res. Clin. Gastroenterol. 16, 933–943 (2002).

Lorimer, J. Gut Buddies. Environ. Humanit. 8, 57–76 (2016).

Kidd, P. M. Multiple sclerosis, an autoimmune inflammatory disease: prospects for its integrative management. Altern. Med. Rev. 6, 540–566 (2001).

Jurjus, A. R., Khoury, N. N. & Reimund, J.-M. Animal models of inflammatory bowel disease. J. Pharmacol. Toxicol. Methods 50, 81–92 (2004).

Abreu, M. T. The pathogenesis of inflammatory bowel disease: Translational implications for clinicians. Curr. Gastroenterol. Rep. 4, 481–489 (2002).

Molodecky, N. A. et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. Gastroenterology 142, 46-54.e42 (2012).

Tontini, G. E. Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives. World J. Gastroenterol. 21, 21 (2015).

McFarland, L. V. State-of-the-art of irritable bowel syndrome and inflammatory bowel disease research in 2008. World J. Gastroenterol. 14, 2625 (2008).

Ray, G. Inflammatory bowel disease in India - Past, present and future. World J. Gastroenterol. 22, 8123 (2016).

Gershwin, M. E. & Mackay, I. R. The causes of primary biliary cirrhosis: Convenient and inconvenient truths. Hepatology 47, 737–745 (2007).

Riddle, M. S., Tribble, D. R., Cachafiero, S. P., Putnam, S. D. & Hooper, T. I. Development of a travelers' diarrhea vaccine for the military: How much is an ounce of prevention really worth? Vaccine 26, 2490–2502 (2008).

Loddo, I. & Romano, C. Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. Front. Immunol. 6, (2015).

Zhang, Y.-Z. Inflammatory bowel disease: Pathogenesis. World J. Gastroenterol. 20, 91 (2014).

Moreira, L. O. & Zamboni, D. S. NOD1 and NOD2 Signaling in Infection and Inflammation. Front. Immunol. 3, (2012).

YAMAMOTO, T., NAKAHIGASHI, M. & SANIABADI, A. R. Review article: diet and inflammatory bowel disease - epidemiology and treatment. Aliment. Pharmacol. Ther. 30, 99–112 (2009).

Schicho, R. et al. Quantitative Metabolomic Profiling of Serum, Plasma, and Urine by 1 H NMR Spectroscopy Discriminates between Patients with Inflammatory Bowel Disease and Healthy Individuals. J. Proteome Res. 11, 3344–3357 (2012).

Mu, L. et al. Indoor air pollution and risk of lung cancer among Chinese female non-smokers. Cancer Causes Control 24, 439–450 (2013).

Felder, J. B. et al. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. Am. J. Gastroenterol. 95, 1949–1954 (2000).

CIPOLLA, G. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND INFLAMMATORY BOWEL DISEASE: CURRENT PERSPECTIVES. Pharmacol. Res. 46, 1–6 (2002).

Kaufmann, W. E., Worley, P. F., Pegg, J., Bremer, M. & Isakson, P. COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc. Natl. Acad. Sci. 93, 2317–2321 (1996).

Ricciotti, E. & FitzGerald, G. A. Prostaglandins and Inflammation. Arterioscler. Thromb. Vasc. Biol. 31, 986–1000 (2011).

Navabi, S. et al. Influences and Impact of Anxiety and Depression in the Setting of Inflammatory Bowel Disease. Inflamm. Bowel Dis. 24, 2303–2308 (2018).

Pedersen, K. M. et al. Risk of ulcerative colitis and Crohn's disease in smokers lacks causal evidence. Eur. J. Epidemiol. (2021) doi:10.1007/s10654-021-00763-3.

Chou, J.-W. et al. Epidemiology and Clinical Outcomes of Inflammatory Bowel Disease: A Hospital-Based Study in Central Taiwan. Gastroenterol. Res. Pract. 2019, 1–8 (2019).

Han, D. Y., Fraser, A. G., Dryland, P. & Ferguson, L. R. Environmental factors in the development of chronic inflammation: A case–control study on risk factors for Crohn's disease within New Zealand. Mutat. Res. Mol. Mech. Mutagen. 690, 116–122 (2010).

Owczarek, D. Diet and nutritional factors in inflammatory bowel diseases. World J. Gastroenterol. 22, 895 (2016).

Sakamoto, N. et al. Dietary Risk Factors for Inflammatory Bowel Disease. Inflamm. Bowel Dis. 11, 154–163 (2005).

Chan, S. S. M. et al. Carbohydrate Intake in the Etiology of Crohn's Disease and Ulcerative Colitis. Inflamm. Bowel Dis. 20, 2013–2021 (2014).

Reif, S. et al. Pre-illness dietary factors in inflammatory bowel disease. Gut 40, 754–760 (1997).

Ananthakrishnan, A. N. et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut 63, 776–784 (2014).

Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. Gut 58, 1606–1611 (2009).

de Silva, P. S. A., Luben, R., Shrestha, S. S., Khaw, K. T. & Hart, A. R. Dietary arachidonic and oleic acid intake in ulcerative colitis etiology. Eur. J. Gastroenterol. Hepatol. 26, 11–18 (2014).

Zhang, Y.-Z. Inflammatory bowel disease: Pathogenesis. World J. Gastroenterol. 20, 91 (2014).

Amre, D. K. et al. Imbalances in Dietary Consumption of Fatty Acids, Vegetables, and Fruits Are Associated With Risk for Crohn's Disease in Children. Am. J. Gastroenterol. 102, 2016–2025 (2007).

Rossi, T. et al. Drink your prevention: beverages with cancer preventive phytochemicals. Polish Arch. Intern. Med. 124, 713–722 (2014).

Marjoram, L. & Bagnat, M. Infection, Inflammation and Healing in Zebrafish: Intestinal Inflammation. Curr. Pathobiol. Rep. 3, 147–153 (2015).

Quinlivan, V. H. & Farber, S. A. Lipid Uptake, Metabolism, and Transport in the Larval Zebrafish. Front. Endocrinol. (Lausanne). 8, (2017).

Rességuier, J. et al. Specific and Efficient Uptake of Surfactant-Free Poly(Lactic Acid) Nanovaccine Vehicles by Mucosal Dendritic Cells in Adult Zebrafish after Bath Immersion. Front. Immunol. 8, (2017).

Vaz, R. L., Outeiro, T. F. & Ferreira, J. J. Zebrafish as an Animal Model for Drug Discovery in Parkinson's Disease and Other Movement Disorders: A Systematic Review. Front. Neurol. 9, (2018).

Oehlers, S. H. et al. The inflammatory bowel disease (IBD) susceptibility genes NOD1 and NOD2 have conserved anti-bacterial roles in zebrafish. Dis. Model. Mech. 4, 832–841 (2011).

Wallace, K. N., Akhter, S., Smith, E. M., Lorent, K. & Pack, M. Intestinal growth and differentiation in zebrafish. Mech. Dev. 122, 157–173 (2005).

Burkhart, J. G. Fishing for mutations. Nat. Biotechnol. 18, 21–22 (2000).

Madara, J. L. et al. Characterization of Spontaneous Colitis in Cotton-Top Tamarins (Saguinus oedipus) and Its Response to Sulfasalazine. Gastroenterology 88, 13–19 (1985).

Hanauer, S. B. & Pineda, A. A. Introduction. Inflamm. Bowel Dis. 12, S1–S2 (2006).

Lee, J. A. & Renshaw, S. A. Zebrafish screens for new colitis treatments – a bottom-up approach. FEBS J. 284, 399–401 (2017).

Geiger, B. M. et al. Intestinal Upregulation of Melanin-Concentrating Hormone in TNBS-Induced Enterocolitis in Adult Zebrafish. PLoS One 8, e83194 (2013).

Brugman, S. et al. Oxazolone-Induced Enterocolitis in Zebrafish Depends on the Composition of the Intestinal Microbiota. Gastroenterology 137, 1757-1767.e1 (2009).

Fleming, S. M., Weil, R. S., Nagy, Z., Dolan, R. J. & Rees, G. Relating Introspective Accuracy to Individual Differences in Brain Structure. Science (80-.). 329, 1541–1543 (2010).

Oehlers, S. H. et al. A chemical enterocolitis model in zebrafish larvae that is dependent on microbiota and responsive to pharmacological agents. Dev. Dyn. 240, 288–298 (2011).

Oehlers, S. H., Flores, M. V., Hall, C. J., Crosier, K. E. & Crosier, P. S. Retinoic acid suppresses intestinal mucus production and exacerbates experimental enterocolitis. Dis. Model. Mech. (2012) doi:10.1242/dmm.009365.

Goldsmith, R. E., Feygina, I. & Jost, J. T. The Gender Gap in Environmental Attitudes: A System Justification Perspective. in Research, Action and Policy: Addressing the Gendered Impacts of Climate Change 159–171 (Springer Netherlands, 2013). doi:10.1007/978-94-007-5518-5_12.

Espenschied, S. T. et al. Epithelial delamination is protective during pharmaceutical-induced enteropathy. Proc. Natl. Acad. Sci. 116, 16961–16970 (2019).

Hedrera, M. I. et al. Soybean Meal Induces Intestinal Inflammation in Zebrafish Larvae. PLoS One 8, e69983 (2013).

Fuentes-Appelgren, P. et al. Effect of the Dietary Inclusion of Soybean Components on the Innate Immune System in Zebrafish. Zebrafish 11, 41–49 (2014).

Solis, C. J. et al. Intestinal Inflammation Induced by Soybean Meal Ingestion Increases Intestinal Permeability and Neutrophil Turnover Independently of Microbiota in Zebrafish. Front. Immunol. 11, (2020).

Coronado, M., Solis, C. J., Hernandez, P. P. & Feijóo, C. G. Soybean Meal-Induced Intestinal Inflammation in Zebrafish Is T Cell-Dependent and Has a Th17 Cytokine Profile. Front. Immunol. 10, (2019).

Perera, E. & Yúfera, M. Effects of soybean meal on digestive enzymes activity, expression of inflammation-related genes, and chromatin modifications in marine fish (Sparus aurata L.) larvae. Fish Physiol. Biochem. 43, 563–578 (2017).

Ulloa, P. E. et al. Lactoferrin Decreases the Intestinal Inflammation Triggered by a Soybean Meal-Based Diet in Zebrafish. J. Immunol. Res. 2016, 1–10 (2016).

Bravo-Tello, K. et al. Effect of microalgae on intestinal inflammation triggered by soybean meal and bacterial infection in zebrafish. PLoS One 12, e0187696 (2017).

Fehrmann-Cartes, K., Coronado, M., Hernández, A. J., Allende, M. L. & Feijoo, C. G. Anti-inflammatory effects of aloe vera on soy meal-induced intestinal inflammation in zebrafish. Fish Shellfish Immunol. 95, 564–573 (2019).

Wu, J. et al. Igf2bp1 is required for hepatic outgrowth during early liver development in zebrafish. Gene 744, 144632 (2020).

Santos, J. M. A. et al. Exogenous WNT5A and WNT11 proteins rescue CITED2 dysfunction in mouse embryonic stem cells and zebrafish morphants. Cell Death Dis. 10, 582 (2019).

He, Y., Liu, S., Leone, S. & Newburg, D. S. Human colostrum oligosaccharides modulate major immunologic pathways of immature human intestine. Mucosal Immunol. 7, 1326–1339 (2014).

He, M. L., Gibb, D., McKinnon, J. J. & McAllister, T. A. Effect of high dietary levels of canola meal on growth performance, carcass quality and meat fatty acid profiles of feedlot cattle. Can. J. Anim. Sci. 93, 269–280 (2013).

Haarder, S., Kania, P. W., Lindebo Holm, T., Ohtani, M. & Buchmann, K. Comparison of Two Chemically-Induced Colitis-Models in Adult Zebrafish, Using Optical Projection Tomography and Novel Transcriptional Markers. Open J. Immunol. 06, 154–180 (2016).

Chuang, L. et al. Zebrafish modeling of intestinal injury, bacterial exposures, and medications defines epithelial in vivo responses relevant to human inflammatory bowel disease. Dis. Model. Mech. (2019) doi:10.1242/dmm.037432.

Qiao, R. et al. Microplastics induce intestinal inflammation, oxidative stress, and disorders of metabolome and microbiome in zebrafish. Sci. Total Environ. 662, 246–253 (2019).

Holtmann, G. & Talley, N. J. Herbal Medicines for the Treatment of Functional and Inflammatory Bowel Disorders. Clin. Gastroenterol. Hepatol. 13, 422–432 (2015).

Pastorelli, L., De Salvo, C., Mercado, J. R., Vecchi, M. & Pizarro, T. T. Central Role of the Gut Epithelial Barrier in the Pathogenesis of Chronic Intestinal Inflammation: Lessons Learned from Animal Models and Human Genetics. Front. Immunol. 4, (2013).

Dahmen, U. et al. Boswellic acid, a potent antiinflammatory drug, inhibits rejection to the same extent as high dose steroids. Transplant. Proc. 33, 539–541 (2001).

Langmead, L. et al. Antioxidant effects of herbal therapies used by patients with inflammatory bowel disease: an in vitro study. Aliment. Pharmacol. Ther. 16, 197–205 (2002).

LANGMEAD, L. & RAMPTON, D. S. Review article: complementary and alternative therapies for inflammatory bowel disease. Aliment. Pharmacol. Ther. 23, 341–349 (2006).

Mynott, T. L., Crossett, B. & Prathalingam, S. R. Proteolytic Inhibition of Salmonella enterica Serovar Typhimurium-Induced Activation of the Mitogen-Activated Protein Kinases ERK and JNK in Cultured Human Intestinal Cells. Infect. Immun. 70, 86–95 (2002).

Hale, L. P., Greer, P. K. & Sempowski, G. D. Bromelain Treatment Alters Leukocyte Expression of Cell Surface Molecules Involved in Cellular Adhesion and Activation. Clin. Immunol. 104, 183–190 (2002).

Manhart, N. et al. Administration of proteolytic enzymes bromelain and trypsin diminish the number of CD4+ cells and the interferon-γ response in Peyer's patches and spleen in endotoxemic balb/c mice. Cell. Immunol. 215, 113–119 (2002).

HALE, L., GREER, P., TRINH, C. & GOTTFRIED, M. Treatment with oral bromelain decreases colonic inflammation in the IL-10-deficient murine model of inflammatory bowel disease. Clin. Immunol. 116, 135–142 (2005).

Bhatwalkar, S. B. et al. Antibacterial Properties of Organosulfur Compounds of Garlic (Allium sativum). Front. Microbiol. 12, (2021).

Kudo, T. Topical application of glycyrrhizin preparation ameliorates experimentally induced colitis in rats. World J. Gastroenterol. 17, 2223 (2011).

Yuan, H. Anti-inflammatory effect of Diammonium Glycyrrhizinate in a rat model of ulcerative colitis. World J. Gastroenterol. 12, 4578 (2006).

Oeckinghaus, A. & Ghosh, S. The NF- B Family of Transcription Factors and Its Regulation. Cold Spring Harb. Perspect. Biol. 1, a000034–a000034 (2009).

Cheon, J. H. et al. Plant sterol guggulsterone inhibits nuclear factor-κB signaling in intestinal epithelial cells by blocking IκB kinase and ameliorates acute murine colitis. Inflamm. Bowel Dis. 12, 1152–1161 (2006).

Chernyavsky, A. I., Galitovskiy, V., Shchepotin, I. B. & Grando, S. A. Anti-Inflammatory Effects of the Nicotinergic Peptides SLURP-1 and SLURP-2 on Human Intestinal Epithelial Cells and Immunocytes. Biomed Res. Int. 2014, 1–7 (2014).

Wan Saudi, W. S. et al. Neuropeptide S inhibits gastrointestinal motility and increases mucosal permeability through nitric oxide. Am. J. Physiol. Liver Physiol. 309, G625–G634 (2015).

Oh, P.-S. & Lim, K.-T. Plant originated glycoprotein has anti-oxidative and anti-inflammatory effects on dextran sulfate sodium-induced colitis in mouse. J. Biomed. Sci. 13, 549–560 (2006).

Wang, X., Zhao, L., Han, T., Chen, S. & Wang, J. Protective effects of 2,3,5,4′-tetrahydroxystilbene-2-O-beta-d-glucoside, an active component of Polygonum multiflorum Thunb, on experimental colitis in mice. Eur. J. Pharmacol. 578, 339–348 (2008).

Ukil, A., Maity, S. & Das, P. K. Protection from experimental colitis by theaflavin-3,3′-digallate correlates with inhibition of IKK and NF- κ B activation. Br. J. Pharmacol. 149, 121–131 (2006).

Miao, X.-P. et al. Selective cyclooxygenase 2 inhibitors for the treatment of rheumatological manifestations of inflammatory bowel disease. in Cochrane Database of Systematic Reviews (ed. Ouyang, Q.) (John Wiley & Sons, Ltd, 2009). doi:10.1002/14651858.CD007744.

Giannotta, M., Tapete, G., Emmi, G., Silvestri, E. & Milla, M. Thrombosis in inflammatory bowel diseases: what's the link? Thromb. J. 13, 14 (2015).

Pitchford, S. C. Novel uses for anti-platelet agents as anti-inflammatory drugs. Br. J. Pharmacol. 152, 987–1002 (2007)..