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A COMPREHENSIVE REVIEW OF IRRITABLE BOWEL SYNDROME SCREENING MODELS FOR DRUG RESEARCH AND DEVELOPMENT

Ankita Wal[1]*, Pranay Wal[1], Neha Verma[1], Ashish Srivastava[1], Awani K Rai[1], Saurabh Kosey[2]

1. *Department of Pharmacy, Ranveer Singh Institute of Technology (Pharmacy), Kanpur, India.*
2. *Department of Pharmacy Practice, ISF College Moga, Punjab, India.*

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ABSTRACT

IBS is a common digestive disorder (IBS). It is marked by visceral, hypersensitivity, and an alter in bowel habits. It is mostly caused by smoking, stress, variations in gut flora, and genetic variants. Because there is currently no particular treatment to cure IBS, it is critical to evaluate the benefits and drawbacks of existing IBS animal models, utilize these models, and construct better models for drug research and development. The main goal of this paper is to study different models of irritable bowel syndrome to recreate IBS symptoms and find the molecular mechanisms that cause the disorder and utilize them in the development of medications that have the potential to be useful in the treatment of IBS. The report's material was generated from review articles and research papers from 1981 to 2021 using keywords like Stress, Brain-gut axis, Trinitrobenzene sulfonic acid, Acetic acid and so on. IBS has no recognized cause or treatment. so, using these models to build successful IBS medication. The pathogenesis of IBS is still poorly understood and psychosocial stress of various origins has been assigned a significant impact. As psychosocial stressors, animal models such as neonatal mother separation, water avoidance stress, and wrap restraint stress have been created to mimic IBS symptomatology and discover the biological pathways associated with the disease. In addition, other models such as antidiarrheal and anti-inflammatory are also used. The investigation of these models has resulted in the development of medications that may be efficacious in IBS management.

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Introduction

Irritable bowel syndrome (IBS) is an illness that occurs in the stomach and intestine that causes stomach discomfort, stool irregularity, and retention of fluid and gas in the stomach. IBS pervasiveness estimates range from 1.1 percent and 45 percent. it is hugely disruptive to a sufferer's regular lifestyle [1]. Symptoms may range from minor to highly debilitating, and women are 1.5 to 2 times more likely than males. Although there has been no reported death with IBS [2] Nowadays, the fundamental pathophysiological processes of IBS are yet unknown. However, greater epithelial permeability, swelling, visceral sensitivity, and changes in brain-gut connection perform a vital in the development of irritable bowel syndrome [3]. The origin and pathogenesis are yet unknown, reflected in the scarcity and ineffectiveness of present medical interventions. Furthermore, in recent generations, FGIDs were categorized as diseases of brain-gut association, **(Figure 1)** That emphasizing the bidirectional interaction among central and peripheral systems, and offering up novel research opportunities in FGID using anxiety and depression rodent models [4]. It has been shown that various stimuli have a vital impact on the onset and progression of IBS. Animal models mimicking the pathophysiology and signs of IBS are significant for IBS studies and may support the implementation of novel therapies. The majority of IBS animal models are produced using various stress stimuli. IBS animal models are classified into three categories based on the action locations of the stimulators: central stimulus produced animal models, peripheral stimulus produced animal models, and combined central and peripheral stimulus produced complicated animal models. Central stimulation alters brain activity and, as a result, impacts gut function via the brain-gut axis. IBS-like symptoms have been induced by peripheral stimulation via the intestinal nervous system **(Figure 2)**.

Corresponding Author: Ankita Wal; Deparment of Pharmacy, Ranveer Singh Institute of Technology (Pharmacy), Kanpur, India. E-mail: shuklaankita02@gmail.com.

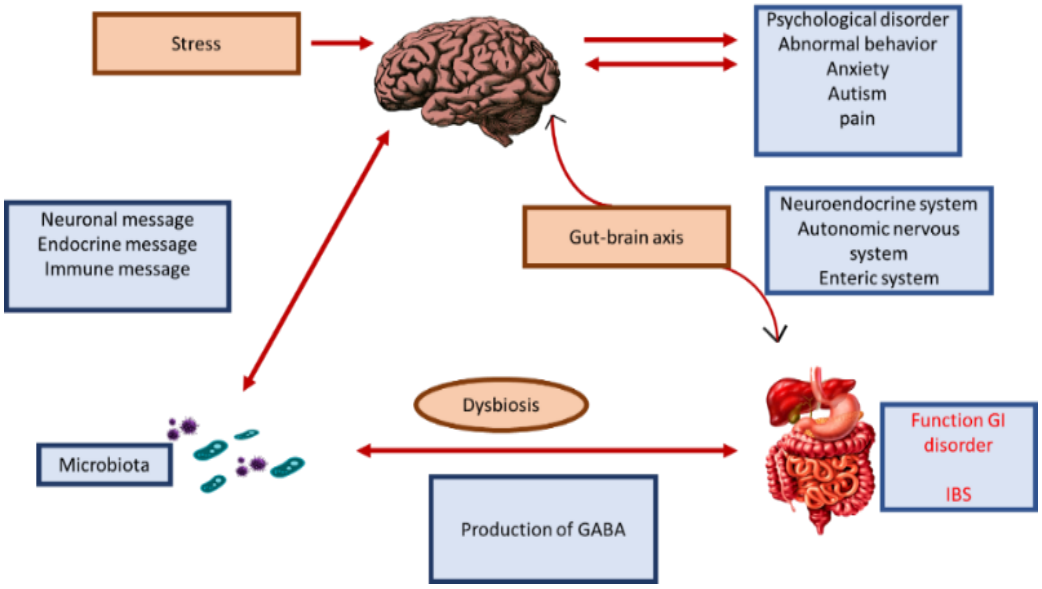

Figure 1. Stress alters brain-gut function and plays a vital role in the development of irritable bowel syndrome

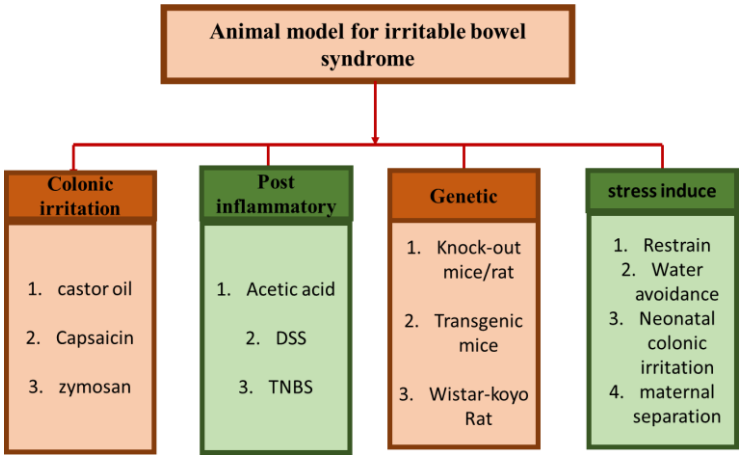

Figure 2. The different Animal models used in the development of irritable bowel syndrome

Stress Related-Model of IBS

Water Avoidance Stress (WAS) Induced Model

Irritable bowel syndrome is commonly caused by mental stress. Prolonged or severe stress likely causes long-term alterations in the central nervous system (CNS), triggering IBS problems [5].

The most common method to construct this model is to put an animal in a Plexiglas tank with a block attached to the ground's center. The tank is full of clean, room-temperature liquid. And the block is 1 cm higher than the water level. The animal is put upon this block for a continuous 1 h daily for a consecutive ten-day. Various studies have found that a 10-day WAS can enhance an animal's visceral hypersensitivity, which is a common symptom of IBS [6-8] **(Figure 3)**.

Brandesi *et al.* [9] introduced this method, which exhibited a brief somatic antinociceptive reaction in conjunction with prolonged visceral hyperalgesia

Da Silva *et al.* [10] improved the methodology for establishing the WAS model by putting the animal on the block for 4 days in a row for 4 hours each day. They discovered that CWAS might cause visceral hypersensitivity and modify gut flora by limiting the growth of Lactobacillus farciminis, as seen in IBS patients. Myers examined rats under 1 hour of stress every day for 7 days in a row and discovered that chronic stress can cause prolonged visceral hypersensitivity, which can be alleviated by glucocorticoid receptor blockers and mineralocorticoid receptor antagonists [11].

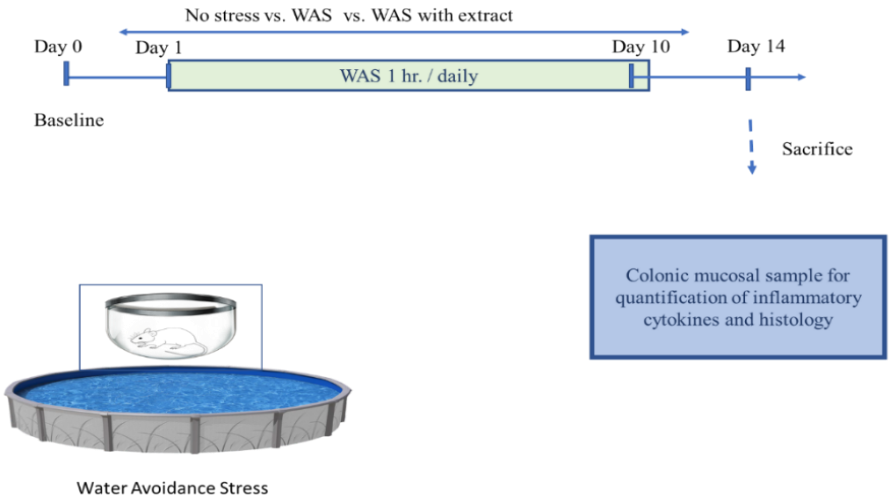

Figure 3. Water avoidance stress (WAS) induced model

Restraint Stress-Induced Animal Model

Williams [12] presented the first restraint stress model, which confined the upper portion of the rat's body for 24 hours. This model demonstrated a reduction of intestinal transport as well as an increase in feces without the development of ulcers. It is regarded as a typical IBS model. Improved restraint stress models are now commonly employed **(Figure 4)**.

Another study performed by, Lv *et al*. gave anesthesia using ether and tied the shoulder, upper arms, and chest of animals with paper tape to avoid itching the head and face for 1 hour, but animals' other behaviors were not restricted. This model demonstrated enhanced colonic movement, higher defecation with loose stools, and visceral sensitivity, indicating that it can be employed for mobility and visceral sensitivity research.

According to Liu *et al*. [13], short-term restraint stress can cause a transitory elevation in reactivity to nociceptive stress but not affect specific muscle cell contraction. Restraint stress can cause certain variations in the gastrointestinal system that are commonly associated with IBS, but it is not suitable for lengthy treatment since it might cause somatic harm.

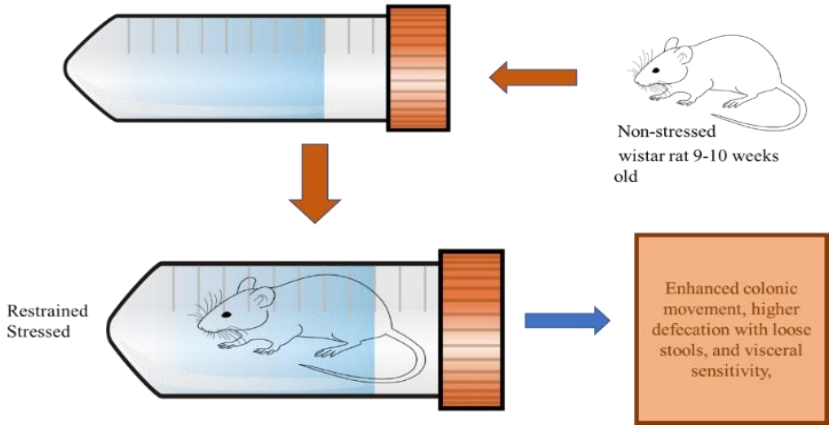

Figure 4. Restraint stress-induced animal model

Neonatal Maternal Separation (NMS) Induced Animal Model

In this method, new-born rats were isolated from their moms for 3 hours every day on postnatal days 2-14. NMS has been shown to cause visceral hypersensitivity as well as alterations in the HPA-axis [14-17]. According to Barouei *et al*. [15], NMS causes higher Adrenocorticotropic Hormone (ACTH) concentrations in plasma and fecal counts of aerobes, anaerobes, enterococci, clostridia, and Escherichia (E. coli), but decreased plasma IgA concentrations.

Another study conducted during postnatal days 2 to 14, by Miquelet *et al*. [16] isolated wild-type C57Bl/AJ babies from their mom for three hours each day, which harmed the fecal Faecalibacterium prausnitzii number. According to Zhou's findings, the amount of Fusobacterium, which can diminish the extent of visceral hypersensitivity, was substantially reduced in C57Bl/AJ mice that received NMS [17].

Colonic Irritation Model of IBS

Castor-Oil Induced Diarrhea

Rats (150-250gm) of any such sex were starved for 18 hours. These are classified into four categories (n=6). Normal saline (2 mL/kg) was given orally to the first category, which served as the control. The standard drug, Loperamide (2 mg/kg) was

treated orally as a preparation for the second category. The test drug was administered orally as a suspension to the third and fourth category at doses of 100 mg/kg and 200 mg/kg, respectively. All rats in each group were given 1ml of castor oil orally following 60 minutes of treatment, and the liquid fecal contents and frequency of bowel movement were recorded for up to 4 hours in the transparent boxes with filter paper at the base. Mass of paper before and after defecation was observed [18] **(Figure 5)**.

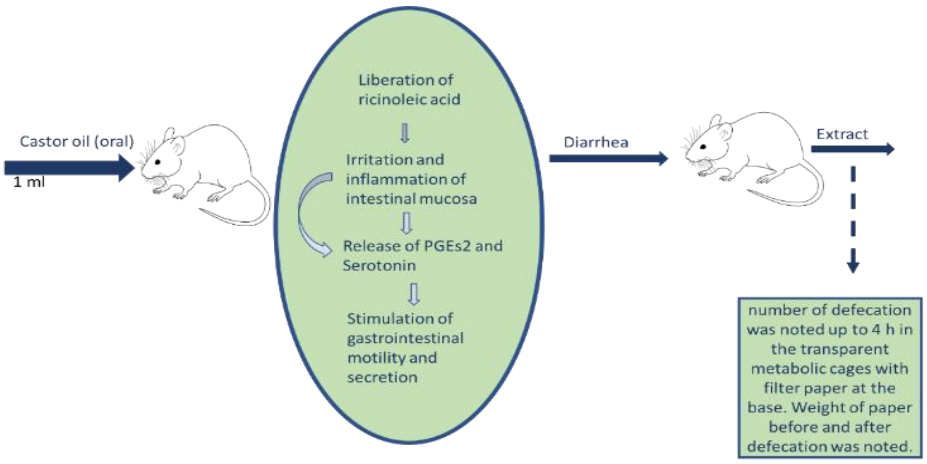

Figure 5. Castor-oil induces colonic irritation that leads to the diarrheal condition

Zymosan-Induced Generalized Inflammation (zigi) Model

Zymosan is a compound generated from the yeast Saccharomyces cerevisiae's cell wall. It is made up of polysaccharide chains of varying molecular masses, with roughly 73% polysaccharides, 15% proteins, and 7% lipids and inorganic components [19]. When injected into animals, it causes inflammation by activating a variety of inflammatory processes [20].

In rodents, a strong zymosan dosage (0.8-1.0 mg/g body mass) administered intraperitoneally causes a three-phase sickness. The rats suffer acute peritonitis after receiving zymosan injections. During the first two days, they are quite unwell, as seen by ruffled fur, frequent bowel movements, sluggish nature, and a decrease in muscle weight. The rodents are leukopenic during this phase, with high oxygen demand [21], myeloperoxidase concentrations (showing neutrophil growth) in the lungs and peritoneum [22, 23], and endothelial permeability [24].

Inflammatory Model of IBS

Nonsteroidal anti-inflammatory medications (NSAIDS) are routinely used to treat inflammatory conditions. However, these medications have a number of side effects, including stomach irritation, ulceration that leads to gastrointestinal bleeding, and perforation. As a result, in recent years, there has been a significant surge in the search for phytochemicals and natural sources with anti-inflammatory characteristics [25]. For example, poncirin administration effectively decreased pain behaviours in all inflammatory pain experimental models, indicating poncirin's promising analgesic potential in inflammatory pain conditions [26].

Acetic Acid-Induced Colitis

Acetic acid-produced colitis is a widely used and conveniently induced model [27-29]. Acetic acid-induced colitis is a model of Irritable bowel syndrome that, in terms of etiology, histological characteristics, and inflammatory mediator profile, is very similar to clinical IBD [30-35] Intrarectal administration of a dilute acetic acid solution causes a non-transmural inflammatory process marked by high neutrophil infiltration into the intestinal tissue, massive cell death of the mucosal and submucosal layers, vascular dilation, edema, and submucosal ulceration, all of which are symptoms of human colitis [33, 35-38] **(Figure 6)**.

It is expected that Protons are generated within the intracellular space by the protonated form of the acid, potentially causing enormous intracellular acidification and severe epithelium damage. To induce colitis with acetic acid, the rodents are anaesthetized by ether and then fasted for 24 hours. Following that, 12 ml of (3-4% acetic acid) is infused 6-5 cm proximal to the anus edge using a medical-grade polyurethane tube for enteral feeding (external diameter 2 mm). After 15-30 seconds of administration, the liquid is removed, and the rodents are slaughtered, then both hemoglobin and colons are taken 24-48 hours following colitis initiation for several histological and biochemical studies [37, 39-43]. Other researchers have shown that intracolonic treatment of 4 ml of 4% acetic acid at a dosage of 5 ml/kg induces colitis in rats [44-48].

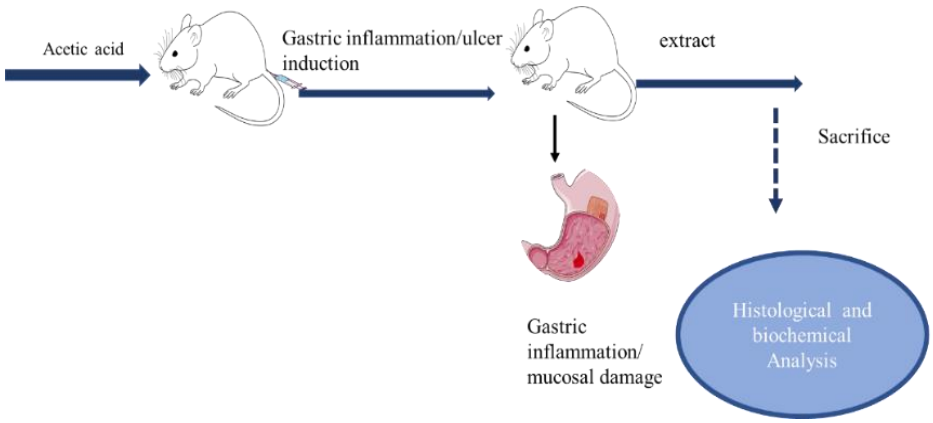

Figure 6. Acetic acid produces inflammation and gastric mucosal damage

Acetic Acid–Induced Writhing Test

The acetic acid–induced abdominal writhing test was performed in mice to assess the peripheral pain response. This approach depends on acetic acid injection to contract the abdominal cavity. 45 minutes after the last medication delivery, 10 mL/kg of 0.6 percent acetic acid solution was administered intravenously. Following the 5-minute waiting time, the number of writhing was recorded for 10 minutes [49].

2, 4, 6-Trinitrobenzene Sulfonic Acid (TNBS)

TNBS promotes transmural swelling in the stomach and evokes cell-mediated immune responses identical to that seen in IBD sufferers [50, 51].

One of the most widely used technique for inducing colitis in rodents includes the use of 10 mg. TNBS was blended with 0.25 mL of 50% ethanol before being infused in male/female Wistar rats through a medical-grade polyurethane catheter (external diameter 2 mm) for enteral feeding at 8 cm proximal to the anal margin. Face-down posture is kept for 13 minutes after hapten installation to minimize leaking and to ensure uniform dispersion of the hapten. Decapitation of rats is performed after 2-6 days of colitis development to measure the extent of colonic inflammation employing several histological and immunohistochemical methods [51, 52]. Various studies have changed the approach by altering the quantity and dosage of TNBS solution, as well as the alcohol content, to produce varying degrees of IBD in Sprague Dawley or Wistar rats of either gender.

Miscellaneous Models of Irritable Bowel Syndrome

Many combined animal models have been produced by exposing animals to various stimuli in order to prevent the chance of rats habituating to a single repeating stimulus and to simulate the numerous pathogenetic aspects of IBS. To develop an IBS model, Zhuang *et al*. [53] coupled acetic acid with restraint stress. They discovered that this model exhibited gut visceral hypersensitivity, elevated concentrations of IL-4 and IL-9 in blood and intestinal mucosa, and enhanced mast cell degranulation.

Spread bury *et al*. [54] discovered that persistent WAS stress mixed with C. Rodentium infection increased DRG (dorsal root ganglion) excitability significantly. Because of the complicated etiology and various processes of IBS that are still unknown, it is increasingly important and practical to build more new IBS animal models utilizing integrated technical methods and to employ these novel IBS models for pathophysiologic research and therapeutic development.

Non-Rodent Models of Irritable Bowel Syndrome

Although the majority of the study has focused on rodent models, various species have been employed to examine the pathophysiology of Functional gastrointestinal disorders (FGID), such as irritable bowel syndrome (IBS).

Guinea pigs are an excellent model for studying intestinal motion and the enteric nervous system. The models employed are identical to those reported earlier in rodents, with the addition of stress models such as water avoidance and CRH injection [55, 56]. Various pharmacological techniques, such as gavage with mustard oil and serotonin or TRH injection, have been employed in guinea pigs as a model of altered GI transit. Mustard oil, when given orally, causes an increase in transit time in the upper GI (oesophagus) and a drop-in transit time in the lower GI (colon) [57]. Ricin oleic acid-induced guinea pig defecation is inhibited by a particular tachykinin receptor NK2 antagonist [58].

In rabbits, intracolonic Zymosan infusion causes intestinal irritation that is alleviated by a tachykinin NK2 receptor antagonist [59].

Pigs have a similar GI system to humans, with similarly sized anatomy, growth, and diet choice, which are obviously totally distinct in rodents [60]. Furthermore, as compared to rats, the enteric nervous system phenotype is comparable to the human equivalent, with more complex inter-neuronal connections and plexi [61]. Pigs have a more well-developed CNS with a complicated behavioral reaction to psychosocial stimuli [62], making them a better model for the GI tract's response to early

life stress in humans. In pigs, weaning is regarded as a very stressful (both psychological and physical) experience that promotes a gut barrier dysfunction [63].

Behavioural Testing

The rodents were put through psychological tests in the sequence listed below: Y maze, elevated-plus maze, and forced swim test **(Figure 7)**.

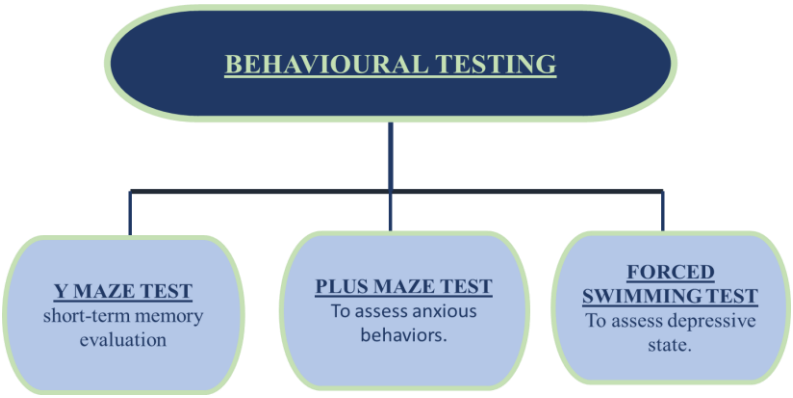

Figure 7. Psychological testing evaluated anxiety and depressive state in rodents

Y-MAZE

The maze test is utilized to examine short-term memory by analyzing the exploration activity of the three sections of the Y-shaped apparatus, as reported by the Kokkinidis group [64]. The maze utilized in this study has 3 sections (40 cm length, 8 cm diameter, and 15 cm tall, all joined at 120-degree angles) and equilateral triangular center space. For 8 minutes, the rat was put at the end of one section and permitted to travel in the maze openly. We used the spontaneous alternation indicator to test short-term memory.

Elevated-Plus Maze

To examine apprehensive behaviors, the elevated maze experiment (EPM) was used, which consisted of a cross-like four-section device set 50 cm above from floor having two sections surrounded with 30 cm high fences and the other two uncovered. The rat was put there at intersection of the open and closed section and given 5 minutes to travel in the maze. During this period, the Pellow group observed the entry and spending time in each section, as well as traveling sessions, for symptoms of anxiousness during a 5-minute test [65].

Forced Swim Test

An altered version of Porsolt's forced swim test (FST) for rodents was used to detect behavioral distress. The technique entails keeping the animals in a transparent cylindrical glass (30 cm wide, 59 cm tall) covered in liquid (15 cm, 26 °C). while the swimming movement of the escape behavior are evaluated. The rodents are subjected to test settings for six minutes, with the first two min dedicated to acclimatization and the final four minutes dedicated to evaluating a sequence of behavioral parameters that indicate depression: swimming, inactivity (floating), and striving behavior [66].

Conclusion

IBS's pathophysiology is complicated and not entirely understood because it is multifaceted. Human participants are forbidden from intervention research. Animal models help study the pathophysiology of IBS without the risks associated with human studies. Every model has advantages and disadvantages. The principal purpose of this review is to provide an overview of IBS models that investigators may employ for their gastrointestinal protection investigations. Following a review of IBS models, we discovered that the models mentioned above are frequently used based on pharmacological requirements, and the model chosen is also influenced by the model's outcome and time. The investigation of these models has resulted in the development of medications that may be efficacious in IBS management.

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