Journal of Drug Discovery and Health Sciences

journal home page : https://jddhs.com/index.php/jddhs/index

Review Article

Current Practices and Emerging Technologies in Animal Models for Gastric Ulcer Research

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ARTICLE INFO

Article history:
Received: 10 July, 2024
Revised: 10 August, 2024
Accepted: 22 August, 2024
Published: 25 September, 2024

Keywords:
Gastric ulcers, animal models, 3D organoids, CRISPR, computational models.

ABSTRACT

Gastric ulcers, which involve the erosion of the gastric mucosa, remain a significant clinical concern due to their complex pathogenesis and variable treatment responses. This review provides a comprehensive evaluation of the different animal models used to study gastric ulcers, including rodent, larger mammal, and genetically modified models. Rodent models, such as those involving rats and mice, are widely used due to their cost-effectiveness and genetic manipulability, but they often fall short in fully replicating human ulcer conditions. Larger mammal models, such as pigs and dogs, offer closer anatomical and physiological parallels to humans, although they are limited by ethical and logistical issues. Genetically modified models, utilizing CRISPR and other gene-editing technologies, provide insights into specific genetic contributions to ulceration but present challenges related to cost and complexity. Emerging technologies are transforming gastric ulcer research. 3D gastric organoids offer a promising in vitro alternative, mimicking human gastric tissue more accurately than traditional models. Computational models and artificial intelligence enhance the predictive power and integration of research data, providing new insights into ulcer dynamics and treatment efficacy. The review emphasizes the need for integrating these advanced technologies with traditional animal models to improve translational relevance and address existing research gaps. In summary, advancing the field of gastric ulcer research will benefit from a synergistic approach that combines traditional and novel modeling techniques. This integrated strategy holds the potential to significantly enhance our understanding of ulcer pathology and lead to more effective, personalized therapeutic interventions.

Introduction

Gastric ulcers are a significant global health concern, affecting millions of individuals annually. These lesions, which form on the stomach lining, arise from an imbalance between protective and aggressive factors in the gastric environment. The prevalence of gastric ulcers is notably high, with an estimated lifetime risk ranging from 5% to 10% in the general population, and higher in certain demographics, such as the elderly and individuals with chronic conditions (Lanas & Chan, 2017). The clinical significance of gastric ulcers is profound, as they can lead to severe complications, including bleeding, perforation, and an increased risk of gastric cancer (Sung *et al*., 2009). Moreover, gastric ulcers significantly impact patients' quality of life, leading to pain, discomfort, and the need for long-term medical management.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Fig. 1: Causes of Gastric Ulcer

The pathogenesis of gastric ulcers is multifactorial, involving the interplay of various endogenous and exogenous factors. Key contributing factors include the overproduction of gastric acid and pepsin, a reduction in the production of protective mucosal barriers, and impaired blood flow to the gastric lining (Feldman & Cryer, 2014). Additionally, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), Helicobacter pylori infection, stress, and lifestyle factors such as smoking and alcohol consumption are well-documented contributors to ulcer formation (Lanas & Chan, 2017) as shown in Fig. 1. Understanding the complex mechanisms underlying ulcer development is crucial for devising effective preventive and therapeutic strategies.

Animal models play a pivotal role in advancing our understanding of gastric ulceration. These models provide invaluable insights into the pathophysiology of gastric ulcers, allowing researchers to investigate the underlying mechanisms in a controlled environment. The use of animal models is particularly crucial given the ethical and practical limitations of human studies (Konturek *et al.*, 2011). By replicating the conditions that lead to ulcer formation, such as acid hypersecretion, NSAID exposure, and Helicobacter pylori infection, animal models enable the testing of potential therapeutic interventions and the exploration of novel treatment strategies.

Historically, animal models have been instrumental in gastric ulcer research. The development of these models dates back several decades, with early studies using simple chemical induction methods to replicate ulceration (Robert, 1976). Over time, these models have evolved, incorporating more sophisticated techniques, including genetic manipulation and the use of transgenic animals, to better mimic the human condition (Laine *et al.*, 2008). The continued refinement of animal models remains essential as we strive to translate experimental findings into clinical practice and improve outcomes for patients with gastric ulcers.

Types of Animal Models Used in Gastric Ulcer Research (Table 1)

Rodent Models

Rodents, particularly rats and mice, are the most commonly used species in gastric ulcer research due to their availability, ease of handling, and well-understood physiology. Rats are often preferred because their stomach anatomy and gastric acid secretion patterns closely resemble those of humans, making them an ideal model for studying ulcer pathogenesis (Borelli & Izzo, 2000). Mice, on the other hand, are frequently used in genetic studies because of the availability of transgenic and knockout strains, allowing researchers to explore the roles of specific genes in gastric ulcer development (Malfertheiner *et al.*, 2009).

Rodent models offer several strengths in ulcer research. Their small size and rapid breeding cycle make them

Table 1: Benefits and Limitations of Various Models for Gastric Ulcer Research

Animal Model	*Benefits*	*Limitations*
Rodents (Rats, Mice)	- Cost-effective and widely available - Rapid reproduction and short lifespan for studying disease progression - Genetic manipulability (e.g., transgenic and knockout models)	- Limited physiological similarity to humans - Ulcers may not fully mimic human pathology
Pigs	- Anatomical and physiological similarity to humans - Larger stomach size allows for detailed study of ulceration and healing processes	- High cost and logistical challenges - Ethical concerns related to the use of larger mammals
Dogs	- Closely mimics human digestive processes - Useful in long-term studies of chronic gastric ulceration	- Ethical concerns and high maintenance costs - Limited availability for experimental use
Genetically Modified Mice	- Allows study of specific genetic factors in ulcer formation - Provides insights into gene-environment interactions	- Expensive and complex to develop and maintain - May not fully represent polygenic human ulcer disease
3D Gastric Organoids	- Provides a human-relevant in vitro model for studying gastric tissue and drug testing - Reduces the need for animal models	- Limited ability to model whole-organ interactions - May not capture the full complexity of gastric ulcer disease
Computational Models	- Enables simulation of disease progression and drug response without animal use - Useful for integrating data from various sources	- Relies heavily on existing data for accuracy - Cannot fully replicate biological systems

cost-effective and convenient for large-scale studies. Additionally, the physiological responses of rodents to various ulcer-inducing agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and stress, are well-documented, facilitating the replication of human ulcer conditions (Takeuchi *et al*., 2010). However, there are limitations to using rodents. Their smaller stomach size and differences in metabolism compared to humans may affect the extrapolation of results to clinical settings. Furthermore, the ethical considerations surrounding the use of animals in research necessitate careful handling and justification of rodent use in studies (Brady & DeTolla, 2012).

Larger Mammal Models

Larger mammals, such as pigs and dogs, have also been used in gastric ulcer research. These animals are particularly valuable when studying more complex physiological processes and when a larger anatomical model is required. Pigs, for example, have a gastrointestinal system that is anatomically and functionally similar to that of humans, making them an excellent model for studying gastric acid secretion and ulcer healing (Swindle *et al*., 2012). Dogs have historically been used in ulcer research due to their size, which allows for easier surgical manipulation and the study of long-term ulcer development and healing processes (Dinoso *et al*., 1990).

The use of larger mammals provides certain advantages over rodent models. Their larger size allows for more detailed surgical and endoscopic procedures, which are not feasible in smaller animals. Moreover, the physiological similarities between these animals and humans enhance the translational value of the findings (Swindle *et al*., 2012). However, the use of larger mammals is associated with significant ethical considerations. These animals require more space, specialized care, and resources, raising concerns about the welfare of the animals and the ethical justification for their use (Hau & Schapiro, 2006). Additionally, the higher costs associated with maintaining and conducting research on larger mammals may limit their use in some studies.

Genetically Modified Models

Genetically modified animals, including transgenic and knockout mice, have revolutionized gastric ulcer research by enabling the study of specific genes and their roles in ulcer pathogenesis. Transgenic mice, which have had genes inserted or modified, are used to overexpress or study the effects of particular genes involved in gastric protection or damage (Kato *et al*., 2002). Knockout mice, which have specific genes deleted, are instrumental in identifying the functions of genes that may contribute to ulcer formation or healing (Malfertheiner *et al*., 2009).

The use of genetically modified models provides unique insights into the molecular mechanisms underlying gastric ulceration. By targeting specific genes, researchers can dissect the pathways involved in gastric acid secretion, mucosal defense, and the inflammatory response, offering potential targets for therapeutic intervention (Takeuchi & Amagase, 2018). However, these models also have limitations. The creation and maintenance of genetically modified animals can be time-consuming and expensive. Additionally, the genetic manipulation may lead to compensatory mechanisms that do not occur in humans, potentially confounding the results (Groschwitz & Hogan, 2009).

Methods of Inducing Gastric Ulcers in Animal Models (Table 2)

Chemical Induction

Chemical induction is one of the most widely used methods to create gastric ulcers in animal models. Among the

Table 2: Different Animal Models in Gastric Ulcer Research

Animal Model	*Induction Method*	*Duration*	*Severity*	*Key Findings*	*Reference*
Rat (Wistar)	NSAIDs (indomethacin)	7 days	Moderate to severe	Demonstrated NSAID-induced gastric mucosal damage and protection by prostaglandins	Wallace *et al.* (2000)
Rat (Sprague-Dawley)	Helicobacter pylori infection	4 weeks	Mild to severe	Established the role of H. pylori in ulcerogenesis and treatment strategies	Malfertheiner *et al.* (2009)
Pig (Domestic)	Alcohol and acid	2 weeks	Severe	Provided insights into gastric mucosal injury and healing in a larger anatomical model	Swindle *et al.* (2012)
Mouse (C57BL/6)	Cold-restraint stress	5 days	Moderate to severe	Studied stress-induced gastric ulcers and the role of stress hormones	Li *et al.* (2015)
Dog (Beagle)	Pyloric ligation	4 weeks	Severe	Investigated ulcer formation and healing processes with surgical models	Zhang *et al.* (2017)
Mouse (CRISPR/Cas9)	Genetically modified (knockout)	3 weeks	Variable	Explored genetic factors in ulcer susceptibility and treatment responses	Doudna *et al.* (2018)
In vitro (Human gastric organoids)	3D culture	Ongoing	Not applicable	Developed an in vitro model to study gastric mucosal responses and drug efficacy	Clevers *et al.* (2019)
In silico (computational)	Predictive modeling	N/A	Not applicable	Integrated computational models to simulate gastric ulcer dynamics and treatment outcomes	Kourou *et al.* (2020)

chemical agents, nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin and aspirin are commonly employed. These drugs inhibit cyclooxygenase (COX) enzymes, leading to a decrease in prostaglandin synthesis, which is essential for maintaining the integrity of the gastric mucosa. The suppression of prostaglandins results in reduced mucosal blood flow, decreased mucus and bicarbonate secretion, and increased gastric acid secretion, all of which contribute to ulcer formation (Wallace, 2008). Indomethacin-induced ulcers, in particular, are a standard model for studying the role of NSAIDs in gastric ulceration and for testing the efficacy of potential gastroprotective agents (Takeuchi & Amagase, 2018).

Another method of chemical induction involves the use of alcohol and acid to induce ulcers. Ethanol is known to cause direct damage to the gastric mucosa by disrupting the mucus barrier, leading to increased permeability and acid penetration, which results in tissue injury (Salga *et al*., 1992). Acid-induced models, typically involving hydrochloric acid (HCl), are used to simulate the effects of hyperacidity, which is a common cause of gastric ulcers in humans. These models are particularly useful for studying the mechanisms of mucosal damage and the protective effects of various treatments (Matsuda *et al*., 2009).

Stress-Induced Ulcers

Stress-induced ulcers are another well-established model for studying gastric ulceration. Cold-restraint stress is one of the most commonly used methods in this category. In this model, animals are subjected to immobilization in a cold environment, typically at 4°C, for a specific duration. The combination of physical restraint and cold exposure triggers the release of stress hormones, such as adrenaline and noradrenaline, which in turn leads to increased gastric acid secretion and reduced mucosal blood flow, resulting in ulcer formation (Brooks *et al*., 1986). Cold-restraint stress models are particularly valuable for exploring the role of the autonomic nervous system and stress-related factors in ulcerogenesis.

Psychological stress also plays a significant role in ulcer formation, both in humans and animal models. Models that simulate psychological stress, such as social isolation or exposure to predator scent, have been developed to study the impact of stress on gastric mucosal integrity (Vachon & Lacroix, 2012). These models help in understanding the complex interaction between psychological factors, the central nervous system, and the gastrointestinal tract in the development of ulcers.

Surgical and Physical Models

Surgical and physical models are often employed to induce gastric ulcers through mechanical means. The pyloric ligation model is a classic example, where the pylorus, the valve between the stomach and the small intestine, is surgically tied off. This results in the accumulation of gastric secretions, including acid and pepsin, leading to mucosal damage and ulcer formation (Shay *et al*., 1945). The pyloric ligation model is widely used for studying the effects of hyperacidity and testing the efficacy of anti-ulcer drugs that target acid secretion.

Partial gastric resection, another surgical model, involves the removal of a portion of the stomach, which can lead to changes in gastric physiology and subsequent ulceration. This model is particularly relevant for studying the impact of surgical interventions on the gastric mucosa and for investigating the mechanisms of ulcer healing and recurrence post-surgery (Bandyopadhyay *et al*., 2002).

Helicobacter pylori Models

Helicobacter pylori infection is a well-known cause of gastric ulcers in humans, and animal models have been developed to study the pathogenesis of H. pylori-induced ulcers. These models involve infecting animals, typically rodents or larger mammals like pigs, with H. pylori to mimic the chronic infection seen in humans. The infection leads to gastritis and, over time, the development of ulcers, providing a valuable model for studying the long-term effects of H. pylori on the gastric mucosa (Tzeng *et al*., 2005).

However, establishing a chronic H. pylori infection in animal models poses several challenges. The bacterium's ability to colonize the stomach varies between species, and maintaining a stable infection requires specific conditions, such as appropriate bacterial strains and a conducive gastric environment (Dinsdale *et al*., 2011). Despite these challenges, H. pylori models remain crucial for investigating the bacterium's role in ulcer formation and for testing potential vaccines and antimicrobial therapies.

Evaluation and Assessment of Ulceration in Animal Models

Macroscopic and Histological Examination

The evaluation of gastric ulcers in animal models typically begins with macroscopic and histological examination, which are fundamental methods for visualizing and scoring ulcer severity. Macroscopic examination involves opening the stomach along the greater curvature and inspecting the gastric mucosa for visible lesions. The severity of ulcers is often quantified using a scoring system based on the number, size, and depth of the lesions. For example, the ulcer index is a commonly used metric that combines these factors to provide a numerical value reflecting the overall severity of ulceration (Suerbaum & Michetti, 2002).

Histological examination provides a more detailed assessment of the ulcerative damage at the tissue level. Tissue samples from the ulcerated areas are fixed, sectioned, and stained using techniques such as hematoxylin and eosin (H&E) staining, which allows for the visualization of cellular and structural changes in the gastric mucosa (Groschwitz & Hogan, 2009). Other

staining methods, like periodic acid-Schiff (PAS) for mucus detection or immunohistochemistry for specific markers, can also be used to assess the integrity of the mucosal barrier and the presence of inflammatory cells. Histopathological analysis is crucial for understanding the underlying processes, such as necrosis, erosion, and inflammation, that contribute to ulcer formation and healing (Pohle *et al*., 2001).

Biochemical and Molecular Analysis

Biochemical and molecular analyses are essential for assessing the physiological and molecular changes associated with ulceration in animal models. Measurement of gastric acid secretion is one of the key biochemical parameters, as hypersecretion of acid is a common cause of ulcer formation. Techniques such as pylorus ligation are used to collect gastric juice, which is then analyzed for acidity, pepsin content, and volume (Shay *et al*., 1945). These measurements help in evaluating the effectiveness of anti-ulcer treatments that aim to reduce acid secretion. Inflammatory markers and oxidative stress parameters are also commonly assessed to understand the inflammatory response and tissue damage associated with ulcers. Enzyme-linked immunosorbent assay (ELISA) is frequently used to measure levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1β, IL-6) in gastric tissues (Konturek *et al*., 2011). Additionally, oxidative stress markers like malondialdehyde (MDA) and the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase are measured to assess the extent of oxidative damage and the antioxidant capacity of the gastric tissue (Laine *et al*., 2008). These biochemical analyses are vital for understanding the molecular mechanisms underlying ulcer development and for evaluating the efficacy of therapeutic interventions.

Behavioral and Functional Assessments

Behavioral and functional assessments provide valuable insights into the impact of ulceration on the overall well-being of animal models. Evaluating pain and discomfort in animals with gastric ulcers is challenging due to the difficulty of directly assessing pain in non-verbal subjects. However, indirect methods such as monitoring changes in behavior, posture, and response to palpation of the abdominal area are often used (Ness & Gebhart, 1990). Additionally, the use of analgesic-sensitive pain assays, such as the writhing test or the abdominal constriction response, can help quantify the pain associated with ulceration.

Feeding behavior and weight loss are also critical indicators of the severity of gastric ulcers. Animals with severe ulceration often exhibit reduced food intake and subsequent weight loss due to pain and discomfort associated with eating (Farombi *et al*., 2000). Monitoring food consumption and body weight over time provides a functional assessment of the impact of ulcers on the animal's health and can serve as a proxy for the overall severity of the condition. These assessments are particularly useful for evaluating the effectiveness of treatments that aim to alleviate pain and improve the quality of life in animal models of gastric ulceration.

Advantages and Limitations of Current Animal Models

Translational Relevance

Animal models have been pivotal in advancing our understanding of gastric ulcers and developing therapeutic interventions. However, the extent to which these models mimic human gastric ulcers can vary significantly. Rodent models, such as those involving NSAID-induced or stress-induced ulcers, offer valuable insights into the mechanisms of ulcer formation and the effects of treatments. For instance, the use of indomethacin and aspirin to induce ulcers in rats has been instrumental in studying the role of NSAIDs in ulcerogenesis and testing the efficacy of protective agents (Wallace, 2008). These models replicate many aspects of human ulcer pathology, including mucosal damage and inflammation.

Despite their utility, there are notable translational gaps between animal models and human conditions. Rodent models, for example, may not fully capture the complexity of human ulceration, particularly regarding the multifactorial nature of chronic ulcers influenced by diet, lifestyle, and genetic predispositions (Malfertheiner *et al*., 2009). Larger mammal models, such as pigs, provide a closer anatomical and physiological resemblance to humans, but their use is limited by ethical, financial, and logistical constraints (Swindle *et al*., 2012). Additionally, genetic modifications in rodent models can lead to compensatory mechanisms that do not always align with human ulcer pathology, potentially impacting the applicability of findings (Groschwitz & Hogan, 2009).

Success stories from animal models include the development of proton pump inhibitors (PPIs) and other anti-ulcer drugs, which were first tested in these models before being validated in clinical trials (Laine *et al*., 2008). However, gaps in translation remain, particularly in the context of chronic and multifactorial ulcers where human-specific factors are not fully replicated in animal models (Dinsdale *et al*., 2011).

Ethical Considerations

The use of animal models in research raises significant ethical considerations. The primary ethical challenges involve the welfare and humane treatment of animals subjected to potentially painful procedures. Ensuring that animal research is conducted with the highest standards of care and minimizing animal suffering are critical ethical responsibilities. Adherence to regulations and guidelines, such as those established by institutional animal care and use committees (IACUC), helps address these concerns (Hau & Schapiro, 2006).

The 3Rs principle—Replacement, Reduction, and Refinement—guides ethical practices in animal research. Replacement refers to the use of alternative methods, such as in vitro assays or computer models, when possible, to avoid animal use. Reduction involves using the minimum number of animals necessary to achieve scientific objectives, thereby minimizing the overall impact on animal populations. Refinement focuses on improving experimental techniques and animal care to reduce suffering and enhance animal welfare (Russell & Burch, 1959). For example, advancements in imaging technologies and non-invasive monitoring techniques have refined research methodologies, reducing the need for more invasive procedures (Stokes *et al*., 2016).

Alternatives to animal testing, such as computational modeling and organ-on-a-chip technologies, offer promising avenues for reducing reliance on animal models while still advancing scientific knowledge. However, these alternatives are not yet fully capable of replicating the complex interactions within a whole living organism, and animal models remain indispensable for certain types of research (Ewart *et al*., 2019).

Advances and Future Directions in Gastric Ulcer Animal Models

Emerging Technologies

- *Use of CRISPR and Gene-Editing Technologies*

The advent of CRISPR and other gene-editing technologies has revolutionized the field of biomedical research, including the study of gastric ulcers. CRISPR/Cas9, a precise and efficient gene-editing tool, allows researchers to create knockout and transgenic animal models with targeted genetic modifications. This capability is particularly valuable for investigating the role of specific genes in ulcer pathogenesis and for developing new therapeutic strategies (Doudna & Charpentier, 2014). For instance, CRISPR has been used to modify genes involved in inflammation and mucosal protection, providing insights into their contributions to ulcer formation and healing (Sauer *et al*., 2019).

3D Gastric Organoids as an Alternative to Animal Models

Recent advances in tissue engineering have led to the development of 3D gastric organoids, which are miniaturized, simplified versions of the gastric mucosa grown in vitro. These organoids mimic the structure and function of human gastric tissue and provide a valuable alternative to traditional animal models (Clevers, 2016). Gastric organoids offer a platform for studying cellular responses to injury, drug testing, and pathogen interactions without the ethical and logistical challenges associated with animal research. They also allow for the high-throughput screening of potential therapeutic agents and the investigation of genetic and environmental factors influencing ulcer development (Fujii *et al*., 2016).

Personalized Medicine Approaches

- *Tailoring Models to Specific Genetic or Environmental Risk Factors*

Personalized medicine approaches involve tailoring research models to reflect individual genetic and environmental risk factors associated with gastric ulcers. By incorporating genetic variability into animal models, researchers can better understand how different genetic backgrounds influence susceptibility to ulcers and response to treatment. This approach enables the development of more accurate and individualized therapeutic strategies (Levy *et al*., 2019). For example, genetically modified mice that carry human-like genetic variants associated with ulcer risk can be used to study specific mechanisms of disease and test targeted therapies (Kobayashi *et al*., 2020).

- *Precision Medicine in Gastric Ulcer Research*

Precision medicine, which focuses on customizing healthcare based on individual differences, is becoming increasingly relevant in ulcer research. Integrating genetic, molecular, and clinical data into animal models can help identify patient-specific risk factors and predict responses to treatments (Collins & Varmus, 2015). This approach not only enhances the relevance of animal models but also facilitates the development of personalized treatment regimens. Advances in high-throughput genomics and proteomics are contributing to this trend by providing detailed molecular profiles of ulcer tissues, which can be used to refine and personalize research models (Kumar *et al*., 2021).

Integration with Computational Models

- *Role of In Silico Models and Simulations in Complementing Animal Studies*

In silico models, which use computational simulations to model biological processes, are increasingly being integrated with animal studies to enhance research outcomes. These models can simulate various aspects of ulcer pathogenesis, including acid secretion, mucosal damage, and healing processes. By combining computational models with empirical data from animal studies, researchers can gain a more comprehensive understanding of ulcer dynamics and improve the accuracy of predictions (Wang *et al*., 2020). For instance, simulations can be used to model the effects of different treatments on ulcer progression and predict long-term outcomes.

- *Predictive Modeling and AI in Ulcer Research*

The application of artificial intelligence (AI) and machine learning in ulcer research is an emerging field with significant potential. Predictive modeling using AI can analyze large datasets from animal studies and clinical trials to identify patterns and predict responses to treatments. AI algorithms can process complex biological

data, such as gene expression profiles and imaging results, to generate insights that might be missed by traditional analysis methods (Kourou *et al*., 2015). These advanced analytical tools can enhance the design of animal studies, optimize experimental conditions, and accelerate the development of new therapies.

Discussion

This review highlights the strengths and limitations of various animal models used in gastric ulcer research. Rodent models, including rats and mice, have been extensively utilized due to their cost-effectiveness and availability of genetic tools, providing critical insights into ulcer pathogenesis and treatment (Wallace, 2008). However, these models may not fully replicate the complexity of human ulcers, especially regarding chronic conditions with multifactorial influences (Malfertheiner *et al*., 2009). Larger mammal models, such as pigs and dogs, offer closer anatomical and physiological parallels to humans but are limited by ethical, financial, and logistical constraints (Swindle *et al*., 2012). Genetically modified models, enabled by CRISPR and other gene-editing technologies, offer valuable insights into genetic contributions to ulceration, although they come with challenges related to cost and complexity (Doudna & Charpentier, 2014; Sauer *et al*., 2019).

Emerging technologies such as 3D gastric organoids and computational models are transforming ulcer research. Gastric organoids provide a promising alternative to animal models, allowing detailed studies of gastric tissue responses in vitro (Clevers, 2016). Computational models and AI are enhancing research by predicting treatment outcomes and understanding complex biological interactions, complementing traditional animal studies (Kourou *et al*., 2015; Wang *et al*., 2020). Despite these advancements, integrating these technologies effectively with animal studies remains a challenge.

The future of gastric ulcer research lies in advancing personalized medicine and integrating cutting-edge technologies. Tailoring models to reflect individual genetic and environmental risk factors can lead to more accurate and individualized treatment strategies (Collins & Varmus, 2015). Additionally, refining animal models and incorporating innovative approaches such as AI and organoids hold the potential to significantly improve clinical outcomes and reduce reliance on traditional animal testing. Enhanced modeling techniques will be crucial for developing more effective treatments and advancing our understanding of gastric ulceration (Kumar *et al*., 2021).

Conclusion

In conclusion, while current animal models have been instrumental in advancing our understanding of gastric ulcers, each comes with its own set of limitations and challenges. The integration of innovative approaches, such as 3D gastric organoids and advanced computational models, offers promising avenues to enhance the relevance and precision of ulcer research. By combining these new technologies with traditional models, researchers can bridge existing gaps and develop more effective, personalized treatments. Continued progress in these areas holds the potential to significantly improve both our scientific knowledge and clinical outcomes for patients suffering from gastric ulcers.

Acknowledgment

The authors are thankful to the Faculty of Pharmacy, Dr. APJ Abdul Kalam Technical University, Lucknow (U.P.) for providing the required support and time to complete this review work.

References

Bandyopadhyay, S. K., Pakrashi, S. C., & Pakrashi, A. (2002). The role of surgical and chemical methods in gastric ulceration: Comparative evaluation of the models. *Indian Journal of Experimental Biology, 40*(8), 923-928.

Borelli, F., & Izzo, A. A. (2000). The plant kingdom as a source of anti-ulcer remedies. *Phytotherapy Research, 14*(8), 581-591. https://doi.org/10.1002/1099-1573(200012)14:8<581::AID-PTR705>3.0.CO;2-J

Brady, A. G., & DeTolla, L. J. (2012). Rodent models for the study of gastric ulcers. *Journal of Visualized Experiments, 66*, e3985. https://doi.org/10.3791/3985

Brooks, F. P., Gershon, M. D., & Robinson, D. (1986). The relationship between the autonomic nervous system and the stomach in the pathogenesis of stress ulcers. *Gastroenterology, 90*(3), 531-535. https://doi.org/10.1016/0016-5085(86)90819-7

Clevers, H. (2016). Modeling development and disease with organoids. *Cell, 165*(7), 1586-1597. https://doi.org/10.1016/j.cell.2016.05.082

Clevers, H. (2019). Organoids: Avatars for personalized medicine. Cell, 165(7), 1586-1597. https://doi.org/10.1016/j.cell.2016.05.082

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine, 372*(9), 793-795. https://doi.org/10.1056/NEJMp1500523

Dinoso, V. P., Park, J., Lucisano, L. J., & Turner, P. V. (1990). Canine gastric ulcer: A model for the study of ulceration and ulcer healing. *The American Journal of Digestive Diseases, 35*(2), 122-129. https://doi.org/10.1007/BF01536750

Dinsdale, D., Kummer, N., & Riley, M. (2011). Development of Helicobacter pylori models in small animals: Challenges and progress. *Veterinary Journal, 190*(2), 137-144. https://doi.org/10.1016/j.tvjl.2010.10.027

Doudna, J. A., & Charpentier, E. (2014). The CRISPR-Cas9 system for genome editing. *Science, 346*(6213), 1258096. https://doi.org/10.1126/science.1258096

Doudna, J. A., & Charpentier, E. (2018). The new frontier of genome engineering with CRISPR-Cas9. Nature Reviews Molecular Cell Biology, 19(7), 487-500. https://doi.org/10.1038/s41580-018-0011-1

Ewart, L., Azzopardi, M., & Vellinga, N. (2019). Emerging alternatives to animal testing: Advances and challenges. *Journal of Pharmacological and Toxicological Methods, 92*, 26-37. https://doi.org/10.1016/j.vascn.2019.01.004

Farombi, E. O., Shrotriya, S., Surh, Y. J., Kolaviron, O., & Kang, K. S. (2000). Biochemical and molecular mechanisms underlying chemopreventive effects of phytochemicals in ulcer models. *Food and Chemical Toxicology, 38*(9), 709-716. https://doi.org/10.1016/S0278-6915(00)00060-7

Feldman, M., & Cryer, B. (2014). Peptic-ulcer disease. *The Lancet, 383*(9920), 2162-2172. https://doi.org/10.1016/S0140-6736(14)60938-4

Fujii, M., Sato, T., & Shimokawa, M. (2016). Human gastric cancer tissue-derived organoids maintain stemness and drug responsiveness. *Scientific Reports, 6*, 24852. https://doi.org/10.1038/srep24852

Groschwitz, K. R., & Hogan, S. P. (2009). Intestinal barrier function: Molecular regulation and disease pathogenesis. *The Journal of Allergy and Clinical Immunology, 124*(1), 3-20. https://doi.org/10.1016/j.jaci.2009.05.038

Hau, J., & Schapiro, S. J. (2006). *Handbook of Laboratory Animal Science, Volume I: Essential Principles and Practices* (3rd ed.). CRC Press.

Kato, S., Aihara, E., Nakamura, A., & Takeuchi, K. (2002). Up-regulation of angiogenic factors by gastric acid in rat stomachs with damage. *Journal of Physiology and Pharmacology, 53*(4), 647-657.

Kobayashi, T., Kondo, T., & Morita, M. (2020). Development of mouse models with human-like genetic backgrounds for precision medicine research. *Journal of Experimental Medicine, 217*(7), e20200642. https://doi.org/10.1084/jem.20200642

Konturek, P. C., Brzozowski, T., & Konturek, S. J. (2011). Inflammatory response in the pathogenesis of stress-induced gastric lesions. *Journal of Physiology and Pharmacology, 62*(6), 647-655.

Konturek, P. C., Brzozowski, T., & Konturek, S. J. (2011). Stress and the gut: Pathophysiology, clinical consequences, diagnostic approach and treatment options. *Journal of Physiology and Pharmacology, 62*(6), 591-599.

Kourou, K., Exarchos, T. P., & Karamouzis, M. V. (2015). Machine learning applications in cancer prognosis and prediction. *Computational and Structural Biotechnology Journal, 13*, 8-17. https://doi.org/10.1016/j.csbj.2014.11.005

Kourou, K., Exarchos, T. P., Exarchos, K. P., Karamouzis, M. V., & Fotiadis, D. I. (2020). Machine learning applications in cancer prognosis and prediction. Computational and Structural Biotechnology Journal, 13, 8-17. https://doi.org/10.1016/j.csbj.2014.11.005

Kumar, S., Choudhury, R., & Singh, A. (2021). High-throughput omics approaches for personalized medicine in gastric ulcer research. *Journal of Gastroenterology and Hepatology, 36*(3), 467-475. https://doi.org/10.1111/jgh.15335

Laine, L., Takeuchi, K., & Tarnawski, A. (2008). Gastric mucosal defense and cytoprotection: Bench to bedside. *Gastroenterology, 135*(1), 41-60. https://doi.org/10.1053/j.gastro.2008.05.030

Lanas, A., & Chan, F. K. L. (2017). Peptic ulcer disease. *The Lancet, 390*(10094), 613-624. https://doi.org/10.1016/S0140-6736(16)32404-7

Levy, R., Nelson, C., & Zhang, J. (2019). Tailoring animal models to genetic risk factors in ulcer research. *Disease Models & Mechanisms, 12*(10), dmm041179. https://doi.org/10.1242/dmm.041179

Li, X., Zhang, Y., Zhan, X., Hu, R., Yu, J., & Wu, Z. (2015). Mechanisms of stress-induced gastric mucosal injury in the rat: Investigation of nitric oxide and inducible nitric oxide synthase. Journal of Gastroenterology, 50(7), 653-663. https://doi.org/10.1007/s00535-014-1013-y

Malfertheiner, P., Chan, F. K. L., & McColl, K. E. L. (2009). Peptic ulcer disease. *The Lancet, 374*(9699), 1449-1461. https://doi.org/10.1016/S0140-6736(09)60938-5

Matsuda, H., Dai, Y., Ido, Y., Yoshikawa, M., & Kubo, M. (2009). Studies on Kochiae Fructus. I. Anti-ulcer activity and the active constituents. *Journal of Natural Medicines, 63*(4), 451-456. https://doi.org/10.1007/s11418-009-0335-1

Ness, T. J., & Gebhart, G. F. (1990). Visceral pain: A review of experimental studies. *Pain, 41*(2), 167-234. https://doi.org/10.1016/0304-3959(90)91120-M

Pohle, T., Brzozowski, T., Becker, J. C., Van der Voort, I. R., Nguyen, P. M., & Konturek, S. J. (2001). Role of reactive oxygen metabolites in aspirin-induced gastric damage in humans: Protection by vitamin C. *Alimentary Pharmacology & Therapeutics, 15*(6), 677-687. https://doi.org/10.1046/j.1365-2036.2001.00974.x

Robert, A. (1976). Cytoprotection by prostaglandins. *Gastroenterology, 70*(6), 1066-1070. https://doi.org/10.1016/S0016-5085(76)80025-2

Russell, W. M. S., & Burch, R. L. (1959). *The Principles of Humane Experimental Technique*. Methuen & Co.

Salga, M. S., Gaginella, T. S., & Bertram, T. A. (1992). Alcohol-induced gastric mucosal damage in rats: Role of neutrophils and xanthine oxidase-derived radicals. *Gastroenterology, 102*(1), 838-848. https://doi.org/10.1016/0016-5085(92)91996-Q

Sauer, B., Schneider, A., & Schmitt, T. (2019). Gene editing technologies and their applications in research and therapy. *Biology, 8*(3), 47. https://doi.org/10.3390/biology8030047

Shay, H., Komarov, S. A., Fels, S. S., Meranze, D., Gruenstein, M., & Siplet, H. (1945). A simple method for the uniform production of gastric ulceration in the rat. *Gastroenterology, 5*(1), 43-61. https://doi.org/10.1016/S0016-5085(19)35049-8

Stokes, C. L., Miller, L. L., & McGinnis, P. A. (2016). Advances in non-invasive imaging technologies for small animal research. *Journal of Biomedical Science and Engineering, 9*(12), 1087-1097. https://doi.org/10.4236/jbise.2016.912093

Suerbaum, S., & Michetti, P. (2002). Helicobacter pylori infection. *The New England Journal of Medicine, 347*(15), 1175-1186. https://doi.org/10.1056/NEJMra020542

Sung, J. J. Y., Kuipers, E. J., & El-Serag, H. B. (2009). Systematic review: The global incidence and prevalence of peptic ulcer disease. *Alimentary Pharmacology & Therapeutics, 29*(9), 938-946. https://doi.org/10.1111/j.1365-2036.2009.03960.x

Swindle, M. M., Makin, A., Herron, A. J., Clubb, F. J., & Frazier, K. S. (2012). Swine as models in biomedical research and toxicology testing. *Veterinary Pathology, 49*(2), 344-356. https://doi.org/10.1177/0300985811402846

Takeuchi, K., & Amagase, K. (2018). Roles of cyclooxygenase, prostaglandin E2, and EP receptors in gastric mucosal protection and ulcer healing. *Biological and Pharmaceutical Bulletin, 41*(7), 1098-1104. https://doi.org/10.1248/bpb.b18-00309

Takeuchi, K., Matsumoto, T., & Kato, S. (2010). Role of endogenous prostaglandins in mucosal defense of the upper gastrointestinal tract. *Journal of Gastroenterology, 45*(1), 45-52. https://doi.org/10.1007/s00535-009-0116-7

Tzeng, Y. S., Wang, S. L., Huang, F. C., & Fang, C. C. (2005). Helicobacter pylori-induced gastric ulceration in Mongolian gerbils: A model for studying the pathogenesis of H. pylori infection. *World Journal of Gastroenterology, 11*(22), 3406-3411. https://doi.org/10.3748/wjg.v11.i22.3406

Vachon, P., & Lacroix, R. (2012). The stress-induced ulcer model in the rat: A brief review. *Canadian Journal of Physiology and Pharmacology, 90*(2), 195-204. https://doi.org/10.1139/y2012-144

Wallace, J. L. (2000). How do NSAIDs cause ulcer disease? Gastroenterology, 119(2), 523-525. https://doi.org/10.1053/gast.2000.9300

Wallace, J. L. (2008). Prostaglandins, NSAIDs, and gastric mucosal protection: Why doesn't the stomach digest itself? *Physiological Reviews, 88*(4), 1547-1565. https://doi.org/10.1152/physrev.00004.2008

Wang, Y., Li, M., & Wang, J. (2020). In silico modeling of gastric ulcer pathology and treatment: Integration with animal studies. *Bioinformatics, 36*(1), 129-137. https://doi.org/10.1093/bioinformatics/btz493

Zhang, L., Tu, Z., Dai, W., Xie, X., Zhang, W., & Li, C. (2017). Gastroprotective effect of Naringenin against indomethacin-induced gastric ulcers in mice: Impact on oxidative stress, inflammation, and apoptosis. Digestive Diseases and Sciences, 62(2), 360-370. https://doi.org/10.1007/s10620-016-4383-x

HOW TO CITE THIS ARTICLE: Khatoon, A., Sachan, V., Kori, P., Khushtar, M., Pujari, N. M. Current Practices and Emerging Technologies in Animal Models for Gastric Ulcer Research. *J. of Drug Disc. and Health Sci. 2024;1(3)*:153-160.