Review Article Open Access
Iranian Journal of Diabetes and Obesity (IJDO)

Orchestrating Metabolic Homeostasis: The Role of Gut Hormones in Next-Generation Therapies for Metabolic Syndrome

Tamer A. Addissouky[1,2,3,4]
[1]Department of Biochemistry, Science Faculty, AL-Mustaqbal University, 51001, Hillah, Babylon, Iraq.
[2]New burg El-Arab Hospital, Ministry of Health, Alexandria, Egypt.
[3]Department of Chemistry, Science Faculty, Menoufia University, Menoufia, Egypt.
[4]American Society for Clinical Pathology (ASCP), Chicago, USA.

Abstract

Metabolic disorders, including obesity and type 2 diabetes, have reached epidemic proportions globally, necessitating novel therapeutic approaches. The gut-brain axis, particularly gut hormones, plays a crucial role in metabolic regulation, offering promising targets for intervention.

This review aims to synthesize current knowledge on gut hormone-based therapies for metabolic disorders, focusing on their mechanisms of action and therapeutic potential.

Gut hormones, including GLP-1, GIP, PYY, ghrelin, and oxyntomodulin, orchestrate complex physiological responses to nutrient intake, influencing insulin secretion, appetite, and energy expenditure. Recent advancements in incretin-based therapies, particularly GLP-1 receptor agonists and dual GLP-1/GIP agonists, have shown remarkable efficacy in improving glycemic control and promoting weight loss. These therapies exploit the synergistic actions of multiple gut hormones, offering a more comprehensive approach to metabolic regulation. Emerging research on PYY analogs and ghrelin antagonists further expands the therapeutic landscape. However, challenges remain in optimizing delivery methods, ensuring long-term efficacy, and mitigating potential side effects.

Gut hormone-based therapies represent a paradigm shift in the management of metabolic disorders. By harnessing the intricate signaling networks of the gut-brain axis, these innovative approaches offer the potential for more effective and targeted interventions in obesity and type 2 diabetes, paving the way for personalized treatment strategies in metabolic medicine.

Keywords:Gut-brain axis, Incretin mimetics, Metabolic syndrome, GLP-1/GIP co-agonists, Enteroendocrine signaling

QR Code:

Citation: Addissouky T A. Orchestrating Metabolic Homeostasis: The Role of Gut Hormones in Next-Generation Therapies for Metabolic Syndrome. IJDO 2025; 17 (2) :130-140

URL: http://ijdo.ssu.ac.ir/article-1-955-en.html

10.18502/ijdo.v17i2.18851

Article info:
Received: 3 January 2025
Accepted: 20 April 2025
Published in May 2025

Corresponding Author:
Tamer A. Addissouky, Department of Biochemistry, Science Faculty, AL-Mustaqbal University, 51001, Hillah, Babylon, Iraq.
Email: tedesoky@science.menofia.edu.eg
Orcid ID: 0000-0003-3797-9155
Tell: (20) 106 640 1396

[DOI: 10.18502/ijdo.v17i2.18851]

Introduction

Overview of metabolic disorders

Metabolic disorders encompass a wide range of conditions, primarily characterized by disruptions in normal metabolic processes. These disorders often involve dysregulation of glucose and lipid metabolism, leading to conditions such as obesity, type 2 diabetes (T2D), and metabolic syndrome (1,2). Obesity is a key driver of various metabolic disorders and is associated with excess adiposity that affects insulin sensitivity and glucose homeostasis. Type 2 Diabetes results from insulin resistance and pancreatic β-cell dysfunction, leading to chronic hyperglycemia. Metabolic syndrome is a clustering of metabolic abnormalities, including central obesity, dyslipidemia, hypertension, and insulin resistance, which together heighten the risk for cardiovascular diseases and T2D (3-5).

The burden of metabolic disorders is staggering, with obesity and T2D reaching epidemic proportions globally. According to the World Health Organization (WHO), over 650 million adults are obese, and the prevalence of diabetes has nearly quadrupled since 1980, affecting over 422 million people worldwide. This surge in metabolic disorders has placed an immense strain on healthcare systems, leading to a rise in comorbidities like cardiovascular disease, kidney failure, and premature mortality (6-11).

Current therapeutic strategies for metabolic disorders, such as lifestyle modifications and pharmacological interventions, have been moderately effective but there are poor long-term adherence, side effects, and lack of sustained efficacy. Thus, there is a pressing need for novel therapeutic approaches that can more effectively target the underlying pathophysiology of these conditions, offering better long-term outcomes with fewer adverse effects (12).

Importance of Gut Hormones in metabolic regulation

The gut-brain axis refers to the complex bidirectional communication between the gastrointestinal (GI) system and the central nervous system (CNS), playing a crucial role in regulating energy intake, nutrient absorption, and glucose homeostasis. Central to this communication are gut hormones, which secreted by enteroendocrine cells in response to nutrient intake and act as key signaling molecules in metabolic regulation (13-15). Gut hormones, including GLP-1, GIP, PYY, ghrelin, and oxyntomodulin, are critical mediators of energy homeostasis, influencing processes such as insulin secretion, appetite control, and gastric emptying. These hormones interact with receptors in both the brain and peripheral tissues, orchestrating a finely tuned response to food intake and energy expenditure. For example, GLP-1, secreted by the L-cells of the small intestine, enhances insulin secretion and reduces appetite, making it a promising target for therapeutic intervention (16-17). Given their pivotal role in metabolic regulation, gut hormone-based therapies have emerged as a novel therapeutic avenue for addressing metabolic disorders. These therapies aim to harness or modulate the activity of gut hormones to improve glucose control, promote weight loss, and restore metabolic balance. This innovative approach holds great potential, particularly in the context of the limitations of current treatments for obesity and T2D (18).

Key Gut Hormones in metabolism

Glucagon-Like Peptide-1 (GLP-1)

Glucagon-like peptide-1 (GLP-1) is a key incretin hormone that significantly influences metabolic processes. It secretes by the intestinal L-cells in response to food intake and plays a critical role in enhancing insulin secretion from pancreatic β-cells in a glucose-dependent manner. This action is crucial in maintaining glucose homeostasis, especially

[DOI: 10.18502/ijdo.v17i2.18851]

postprandial. Additionally, GLP-1 delays gastric emptying, thereby contributing to satiety and appetite regulation, making it a vital hormone in the context of obesity and weight management (19-21). The therapeutic potential of GLP-1 realized with the development of GLP-1 receptor agonists such as liraglutide and semaglutide, which mimic the effects of endogenous GLP-1. These agents have demonstrated significant benefits in improving glycemic control, promoting weight loss, and reducing cardiovascular risk in patients with T2D and obesity. Their ability to address multiple facets of metabolic dysregulation has made them a cornerstone in the treatment of metabolic disorders (22-28).

Glucose- Dependent Insulinotropic Polypeptide (GIP)

Glucose- dependent insulinotropic polypeptide (GIP) is another incretin hormone secreted by the K-cells of the small intestine in response to nutrient ingestion. It stimulates insulin secretion in a glucose-dependent manner, similar to GLP-1, but also plays a unique role in lipid metabolism, promoting fat storage in adipose tissue. This dual role has made GIP a subject of intense research, particularly in understanding its contribution to obesity and insulin resistance (29). Recent advancements have highlighted the potential of dual incretin therapies that combine the effects of GLP-1 and GIP. GLP-1/GIP co-agonists, such as tirzepatide, have shown promising results in promoting superior glycemic control and weight loss compared to GLP-1 agonists alone. These combination therapies may offer a more comprehensive approach to treating metabolic disorders by targeting multiple pathways involved in glucose and lipid metabolism (30-35).

Peptide YY (PYY)

Peptide YY (PYY) is a hormone predominantly secreted by the L-cells in the distal gut, particularly after meals. PYY plays a critical role in appetite suppression and energy balance by acting on receptors in the brain, particularly in the hypothalamus, to reduce food intake. It also slows gastric motility, enhancing the feeling of fullness and reducing subsequent calorie consumption. PYY interacts synergistically with other gut hormones, such as GLP-1, to regulate appetite and energy homeostasis. Its potential as a therapeutic target for obesity, with research focusing on PYY-based interventions, such as PYY analogs and PYY-enhancing stra tegies. However, challenges remain in optimizing its delivery and ensuring sustained efficacy in reducing body weight (36,37).

Ghrelin

Ghrelin, often referred to as the "hunger hormone," secreted primarily by the stomach and plays a fundamental role in stimulating appetite as presented in Table 1. It acts on the hypothalamus to promote hunger and increase food intake, making it a key player in energy homeostasis. Ghrelin levels rise before meals and fall after eating, closely aligning with hunger sensations. Therapeutically, ghrelin antagonists investigated as potential agents for weight loss.

Table 1. Comparison of key gut hormones in metabolic regulation

Gut Hormone	Primary Site of Secretion	Main Physiological Actions	Therapeutic Potential	Current/Potential Drug Examples
GLP-1	L-cells of small intestine	Enhances insulin secretion Reduces appetite Delays gastric emptying	Glycemic control Weight loss Cardiovascular protection	Liraglutide, Semaglutide
GIP	K-cells of small intestine	Stimulates insulin secretion Promotes fat storage	Glycemic control Potential for weight gain (limitation)	Tirzepatide (in combination with GLP-1)
PYY	L-cells of distal gut	Suppresses appetite Slows gastric motility	Weight loss	PYY analogs (in development)
Ghrelin	Stomach	Stimulates appetite Increases food intake	Weight gain (in cachexia) Weight loss (via antagonists)	Ghrelin antagonists (in development)
Oxyntomodulin	L-cells of small intestine	Reduces appetite Increases energy expenditure	Weight loss Glycemic control	Oxyntomodulin analogs (in development)

[DOI: 10.18502/ijdo.v17i2.18851]

By inhibiting ghrelin's action, these antagonists aim to reduce hunger and promote a negative energy balance. Despite the theoretical appeal, the clinical development of ghrelin antagonists has faced hurdles, including the challenge of achieving significant and sustained appetite suppression (38-42).

Oxyntomodulin

Oxyntomodulin is a gut hormone with a dual role in activating both the GLP-1 receptor and the glucagon receptor. This dual action positions oxyntomodulin as a unique modulator of energy balance, with the potential to enhance insulin secretion (via GLP-1 receptor activation) and increase energy expenditure (via glucagon receptor activation). Emerging evidence suggests that oxyntomodulin may have significant potential for weight loss and metabolic improvements, particularly when used in combination with other incretin therapies. However, further researches need to fully understand its mechanism of action and optimize its therapeutic application in metabolic disorders (43,44).

Other Gut Hormones

Several other gut hormones, such as cholecystokinin (CCK) and secretin, play important roles in nutrient digestion and metabolism. CCK released in response to fat and protein intake and stimulates the release of digestive enzymes from the pancreas, as well as bile from the gallbladder, aiding in nutrient digestion. Secretin primarily modulates the secretion of bicarbonate to neutralize stomach acid, facilitating digestion in the small intestine. Recent findings have also shed light on lesser-known gut hormones, such as motilin and neuropeptide Y (NPY), which may have additional roles in regulating metabolic processes. The exploration of these hormones in the context of metabolic regulation is ongoing and may reveal new therapeutic opportunities (45-48).

Mechanisms of Gut Hormone-Based Therapies

Incretin-Based Therapies

Incretin-based therapies have revolutionized the treatment landscape for metabolic disorders, particularly T2D. The most well established class of these therapies is GLP-1 receptor agonists, which enhance insulin secretion, slow gastric emptying, and reduce appetite. Clinical trials have consistently demonstrated their efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk. GIP analogs and GLP-1/GIP dual agonists represent the next frontier in incretin-based therapies. These agents exploit the complementary actions of GLP-1 and GIP on glucose and lipid metabolism, offering potentially superior outcomes in terms of both glycemic control and weight reduction. Early clinical trials of dual agonists, such as tirzepatide, have shown promising results, with substantial improvements in HbA1c and body weight compared to GLP-1 agonists alone (49,50).

Gut Hormone antagonists and inhibitors

The development of ghrelin antagonists has garnered interest as a potential strategy for appetite suppression and weight loss. By blocking ghrelin's action on its receptor, these antagonists aim to reduce hunger and promote negative energy balance. However, clinical trials have revealed challenges in achieving consistent and significant appetite suppression, suggesting that more researches need to optimize these therapies. Other hormone antagonists, such as neuropeptide Y (NPY) antagonists, are under investigation for their potential to reduce food intake and improve metabolic outcomes. NPY is a potent orexigenic peptide that stimulates appetite and promotes energy storage, making it an attractive target for obesity therapies (51-54).

Combination therapies

Combination therapies that target multiple gut hormones simultaneously have shown great promise in the treatment of metabolic

[DOI: 10.18502/ijdo.v17i2.18851]

disorders as presented in Table 2. GLP-1/GIP/glucagon triple agonists represent an exciting development in this field, offering the potential for enhanced metabolic control by addressing multiple pathways involved in glucose and lipid metabolism. Additionally, there is growing interest in the synergistic effects of gut hormone-based therapies with other pharmacological agents, such as SGLT2 inhibitors and insulin sensitizers. These combinations may offer enhanced efficacy and more metabolic benefits **(**55,56**)**.

Clinical applications and current therapeutic agents

GLP-1 Receptor Agonists

GLP-1 receptor agonists have become a cornerstone in the treatment of T2D and obesity. Agents such as semaglutide and dulaglutide have demonstrated robust efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk. These drugs are generally well tolerated, although common side effects include nausea, vomiting, and, in rare cases, pancreatitis. Long-term studies have shown that GLP-1 receptor agonists can lead to sustained weight loss and improvements in glucose control, making them an attractive option for patients with both T2D and obesity. Additionally, their cardiovascular benefits, particularly in reducing major adverse cardiovascular events (MACE), have made them a preferred choice in patients with T2D at high cardiovascular risk **(**57,58**)**.

Dual and Triple Agonists

The development of dual and triple agonists has marked a significant advancement in the treatment of metabolic disorders. Tirzepatide, a dual GLP-1/GIP agonist, has demonstrated superior efficacy in reducing HbA1c and body weight compared to GLP-1 agonists alone. Early clinical trials of triple agonists (GLP-1/GIP/glucagon) show more promising results, with significant improvements in glycemic control, weight loss, and lipid metabolism. As these agents progress through clinical development, they hold the potential to become first-line therapies for patients with complex metabolic disorders, offering comprehensive metabolic benefits that extend beyond what is achievable with current monotherapies (59-62).

Novel Peptide therapies

In addition to incretin-based therapies, novel peptide therapies targeting hormones such as PYY, ghrelin, and oxyntomodulin explored for their potential in treating metabolic disorders. PYY analogs have shown promise in reducing appetite and promoting weight loss, although challenges remain in optimizing their delivery and ensuring sustained efficacy. Ghrelin antagonists and oxyntomodulin analogs are also under investigation, with early studies suggesting potential benefits in weight management and metabolic control.

However, the development of these therapies is still in its early stages, and further researches need to overcome challenges

Table 2. Evolution of gut hormone-based therapies for metabolic disorders

Generation	Therapy Type	Examples	Key Features	Advantages	Limitations
First	Single hormone agonists	GLP-1 RAs (e.g., Liraglutide)	Mimics single gut hormone action	Improved glycemic control Moderate weight loss	Single target Variable efficacy
Second	Dual hormone agonists	GLP-1/GIP co-agonists (e.g., Tirzepatide)	Combines actions of two gut hormones	Enhanced glycemic control Superior weight loss	Potential for increased side effects
Third (Emerging)	Multi-hormone agonists	GLP-1/GIP/Glucagon tri-agonists	Targets multiple metabolic pathways	Potential for greater metabolic improvements Customizable hormone ratios	Complex interactions Still in early development
Fourth (Future)	Personalized gut hormone therapies	Tailored combinations based on individual profiles	Optimizes therapy based on patient-specific gut hormone deficiencies or resistances	Maximized efficacy Minimized side effects	Requires advanced diagnostic tools Higher complexity in treatment planning

[DOI: 10.18502/ijdo.v17i2.18851]

related to drug delivery, bioavailability, and long-term safety (63,64).

Microbiota-Gut Hormone interactions

The gut microbiota plays a critical role in modulating gut hormone levels and, consequently, metabolic regulation. Emerging research suggests that microbiota-targeted therapies, such as probiotics, prebiotics, and fecal microbiota transplantation, may enhance the efficacy of gut hormone-based therapies by restoring the balance of beneficial gut bacteria. These interventions have shown promise in improving metabolic outcomes, particularly in patients with obesity and insulin resistance. By modulating the gut microbiota, it may be possible to enhance the secretion and activity of key gut hormones, offering a novel approach to the treatment of metabolic disorders (65-68).

Challenges and limitations

Pharmacological challenges

One of the major challenges in the development of gut hormone-based therapies is the stability and bioavailability of peptide-based drugs. Peptides are inherently unstable in the gastrointestinal tract, requiring injectable formulations for effective delivery. Attempts to develop oral formulations met limited success due to the rapid degradation of peptides in the stomach and intestines. Additionally, side effects such as nausea and vomiting, particularly with GLP-1 receptor agonists, remain a significant concern. Although these side effects are generally mild and transient, they can influence patient adherence and limit the long-term use of these therapies (69-72).

Individual variability

Genetic and environmental factors play a significant role in determining an individual's response to gut hormone-based therapies. Variations in receptor sensitivity, hormone secretion, and gut microbiota composition can all influence treatment outcomes. This variability underscores the need for a personalized medicine approach that takes into account individual differences to optimize therapy (72-74).

Regulatory and cost issues

The regulatory landscape for gut hormone-based therapies is complex, with stringent requirements for demonstrating safety and efficacy. Additionally, the high cost of gut hormone therapies, particularly GLP-1 receptor agonists and dual agonists, presents a significant barrier to widespread adoption. Ensuring cost-effectiveness and improving accessibility will be critical for the long-term success of these therapies (75-76).

Future directions

Emerging therapies and research

Research into new gut hormone analogs and combination therapies is ongoing, with several promising candidates in the pipeline. Gene therapy and gut hormone modulation through CRISPR and other gene-editing technologies represent exciting new avenues for research, offering the potential to correct metabolic dysregulation at its source (77-80).

Personalized and precision medicine

The future of gut hormone-based therapies lies in personalized and precision medicine. Advances in genetic, epigenetic, and microbiome profiling will enable the tailoring of therapies to individual patients, optimizing efficacy and minimizing side effects. Identifying biomarkers that predict treatment response will be critical for developing personalized treatment protocols (81-84).

Integration of digital health

The integration of digital health technologies, such as wearables and mobile apps, into the management of metabolic disorders will play an increasingly important role in the future. These tools can provide real-time data on metabolic markers, enabling continuous monitoring and adjustments to treatment regimens. Additionally, AI and machine learning will help optimize treatment

[DOI: 10.18502/ijdo.v17i2.18851]

protocols by analyzing data from large patient populations, ultimately improving outcomes for individuals with metabolic disorders (85,86).

Conclusion

This comprehensive review underscores the pivotal role of gut hormones in metabolic regulation and their immense potential as therapeutic targets for metabolic disorders. The remarkable efficacy of GLP-1 receptor agonists and the emerging promise of dual GLP-1/GIP agonists represent significant advancements in the field, offering superior glycemic control and weight loss outcomes compared to traditional therapies. The synergistic actions of multiple gut hormones, as exemplified by these novel therapies, provide a more holistic approach to addressing the complex pathophysiology of obesity and type 2 diabetes. However, while these developments are promising, challenges remain in optimizing delivery methods, ensuring long-term efficacy, and fully elucidating the intricate interplay between various gut hormones. Future research directions should focus on developing more targeted combination therapies, exploring the potential of lesser-studied gut hormones like PYY and oxyntomodulin, and investigating personalized treatment approaches based on individual gut hormone profiles. The limitations of current research, including the need for longer-term safety data and a better understanding of the gut hormone system's adaptability to chronic interventions, highlight the importance of continued investigation in this rapidly evolving field.

Recommendations

To advance the field of gut hormone-based therapies for metabolic disorders, several key recommendations emerge. Firstly, there is a need for large-scale, long-term clinical trials to assess the safety and efficacy of gut hormone modulators, particularly combination therapies, beyond the currently established GLP-1 and GIP agonists. Secondly, research efforts should be towards developing innovative drug delivery systems that can enhance the bioavailability and targeted action of gut hormone-based therapies, potentially exploring oral formulations or long-acting depot preparations. Thirdly, integrating personalized medicine approaches, such as gut hormone profiling and genetic analysis, into treatment strategies could optimize therapeutic outcomes and minimize adverse effects. Additionally, investigating the potential of gut hormone-based therapies in preventing the progression from prediabetes to type 2 diabetes could yield significant public health benefits. Finally, elucidating the complex interactions between gut hormones, the microbiome, and host metabolism could uncover new therapeutic targets and enhance our understanding of metabolic regulation, potentially leading to more comprehensive and effective treatment strategies for metabolic disorders.

Acknowledgments

The author thanks all the researchers who have made great efforts in their studies. Moreover, we are grateful to this journal's editors, reviewers, and readers.

Funding

Corresponding author supplied all study materials. There was no further funding for this study.

Conflict of Interest

The authors have stated no conflict of interest.

Authors' contributions

The Corresponding author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

[DOI: 10.18502/ijdo.v17i2.18851]

References

1. Alemany M. The metabolic syndrome, a human disease. International journal of molecular sciences. 2024;25(4):2251.
2. Khatun MM, Bhuia MS, Chowdhury R, Sheikh S, Ajmee A, Mollah F, et al. Potential utilization of ferulic acid and its derivatives in the management of metabolic diseases and disorders: An insight into mechanisms. Cellular Signalling. 2024;121:111291.
3. Zakynthinos GE, Tsolaki V, Oikonomou E, Vavouranakis M, Siasos G, Zakynthinos E. Metabolic syndrome and atrial fibrillation: different entities or combined disorders. Journal of Personalized Medicine. 2023;13(9):1323.
4. Iafusco D, Franceschi R, Maguolo A, Guercio Nuzio S, Crinò A, Delvecchio M, et al. From metabolic syndrome to type 2 diabetes in youth. Children. 2023;10(3):516.
5. Sobieska K, Buczyńska A, Krętowski AJ, Popławska-Kita A. Iron homeostasis and insulin sensitivity: unraveling the complex interactions. Reviews in Endocrine and Metabolic Disorders. 2024;25(5):925-39.
6. Zhang Y, Gu Z, Xu Y, He M, Gerber BS, Wang Z, et al. Global scientific trends in healthy aging in the early 21st century: A data-driven scientometric and visualized analysis. Heliyon. 2024;10(1): e23405
7. Addissouky TA, Sayed IE, Ali MM, Wang Y, Baz AE, Khalil AA, et al. Latest advances in hepatocellular carcinoma management and prevention through advanced technologies. Egyptian Liver Journal. 2024;14(1):2.
8. Addissouky TA, Ali MM, El Sayed IE, Wang Y, Khalil AA. Translational insights into molecular mechanisms of chemical hepatocarcinogenesis for improved human risk assessment. Advances in Clinical Toxicology. 2024;9(1):294.
9. Addissouky TA, Ali MM, El Sayed IE, Wang Y, El Baz A, Elarabany N, et al. Preclinical promise and clinical challenges for innovative therapies targeting liver fibrogenesis. Archives of Gastroenterology Research. 2023;4(1):14-23.
10. Addissouky TA. Transforming screening, risk stratification, and treatment optimization in chronic liver disease through data science and translational innovation. The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy. 2024;25(1):53-62.
11. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Schisandra chinensis in liver disease: exploring the mechanisms and therapeutic promise of an ancient Chinese botanical. Archives of pharmacology and therapeutics. 2024;6(1):27-33.
12. Lonardo A. The heterogeneity of metabolic syndrome presentation and challenges this causes in its pharmacological management: a narrative review focusing on principal risk modifiers. Expert Review of Clinical Pharmacology. 2023;16(10):891-911.
13. Li S, Liu M, Cao S, Liu B, Li D, Wang Z, Sun H, Cui Y, Shi Y. The mechanism of the gut-brain axis in regulating food intake. Nutrients. 2023;15(17):3728.
14. Lu S, Zhao Q, Guan Y, Sun Z, Li W, Guo S, et al. The communication mechanism of the gut-brain axis and its effect on central nervous system diseases: A systematic review. Biomedicine & Pharmacotherapy. 2024;178:117207.
15. Pan I, Issac PK, Rahman MM, Guru A, Arockiaraj J. Gut-brain axis a key player to control gut dysbiosis in neurological diseases. Molecular Neurobiology. 2024;61(12):9873-91.
16. Roh E, Choi KM. Hormonal gut–brain signaling for the treatment of obesity. International journal of molecular sciences. 2023;24(4):3384.
17. Bany Bakar R, Reimann F, Gribble FM. The intestine as an endocrine organ and the role of gut hormones in metabolic regulation. Nature reviews Gastroenterology & hepatology. 2023;20(12):784-96.
18. Lad SU, Vyas GS, Mohd S, Mishra V, Wadhwa S, Singh S, et al. Recent advances in therapeutic interventions of polycystic ovarian syndrome. Obesity Medicine. 2024;48:100543.
19. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduction and Targeted Therapy. 2024 ;9(1):234.
20. Holst JJ. GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. Nature Metabolism. 2024;6(10):1866-85.
21. Nicze M, Dec A, Borówka M, Krzyżak D, Bołdys A, Bułdak Ł, et al. Molecular Mechanisms behind Obesity and Their Potential Exploitation in Current and Future Therapy. International Journal of Molecular Sciences. 2024;25(15):8202.
22. Lafferty RA, Flatt PR, Irwin N. GLP-1/GIP analogs: potential impact in the landscape of obesity pharmacotherapy. Expert opinion on pharmacotherapy. 2023;24(5):587-97.
23. Mariam Z, Niazi SK. Glucagon-like peptide agonists: a prospective review. Endocrinology, Diabetes & Metabolism. 2024;7(1):e462.
24. Addissouky T, Ali MM, El Sayed IE, Alubiady MH. Realizing the promise of artificial intelligence in hepatocellular carcinoma through opportunities and recommendations for responsible translation. Jurnal Online Informatika. 2024;9(1):70-9.

[DOI: 10.18502/ijdo.v17i2.18851]

25. Addissouky TA, Ali MM, Sayed IE, Wang Y. Emerging advanced approaches for diagnosis and inhibition of liver fibrogenesis. The Egyptian Journal of Internal Medicine. 2024;36(1):19.
26. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Bending the curve through innovations to overcome persistent obstacles in HIV prevention and treatment. Journal of AIDS and HIV Treatment. 2024;6(1):44-53.
27. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH. Optical insights into fibrotic livers: Applications of near-infrared spectroscopy and machine learning. Archives of Gastroenterology Research. 2024;5(1):1-10.
28. Addissouky TA, El Sayed IE, Ali MM, Wang Y, El Baz A, Khalil AA, et al. Can vaccines stop cancer before it starts? Assessing the promise of prophylactic immunization against high-risk preneoplastic lesions. Journal of Cellular Immunology. 2023;5(4):127-40.
29. Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. Diabetologia. 2023;66(10):1765-79.
30. Scheen, A. J. Dual GIP/GLP-1 receptor agonists: New advances for treating type-2 diabetes. Annales D'Endocrinologie, 2023;84(2):316-21.
31. Nogueiras R, Nauck MA, Tschöp MH. Gut hormone co-agonists for the treatment of obesity: from bench to bedside. Nature Metabolism. 2023;5(6):933-44.
32. Addissouky TA, El Sayed IE, Ali MM, Wang Y, El Baz A, Elarabany N, et al. Oxidative stress and inflammation: elucidating mechanisms of smoking-attributable pathology for therapeutic targeting. Bulletin of the National Research Centre. 2024;48(1):16.
33. Addissouky TA. Emerging Therapeutics targeting cellular stress pathways to mitigate end-organ damage in type 1 diabetes. Avicenna Journal of Medical Biochemistry. 2024;12(1):39-46.
34. Addissouky TA, Ali MM, El Sayed IE, Wang Y. Type 1 diabetes mellitus: retrospect and prospect. Bulletin of the National Research Centre. 2024;48(1):42.
35. Addissouky T, Ali M, El Sayed IE, Wang Y. Revolutionary innovations in diabetes research: from biomarkers to genomic medicine. Iranian journal of diabetes and obesity. 2023;15(4):228-42.
36. Xiao Y, Jin L, Zhang C. From a hunger-regulating hormone to an antimicrobial peptide: gastrointestinal derived circulating endocrine hormone-peptide YY exerts exocrine antimicrobial effects against selective gut microbiota. Gut Microbes. 2024;16(1):2316927.
37. Smith KR, Moran TH. Gastrointestinal peptides in eating-related disorders. Physiology & behavior. 2021;238:113456.
38. Nunez-Salces M, Li H, Feinle-Bisset C, Young RL, Page AJ. The regulation of gastric ghrelin secretion. Acta Physiologica. 2021;231(3):e13588.
39. Akalu Y, Molla MD, Dessie G, Ayelign B. Physiological effect of ghrelin on body systems. International journal of endocrinology. 2020;2020(1):1385138.
40. Addissouky TA. Precision medicine for personalized cholecystitis care: integrating molecular diagnostics and biotherapeutics. Bulletin of the National Research Centre. 2024;48(1):89.
41. Addissouky TA, Ali MM, El Sayed IE, Wang Y. Recent advances in diagnosing and treating helicobacter pylori through botanical extracts and advanced technologies. Archives of Pharmacology and Therapeutics. 2023;5(1):53-66.
42. Addissouky TA, Wang Y, El Sayed IE, Baz AE, Ali MM, Khalil AA. Recent trends in Helicobacter pylori management: harnessing the power of AI and other advanced approaches. Beni-Suef University Journal of Basic and Applied Sciences. 2023;12(1):80.
43. Pei Z, Zhou D, Yan J, Wang S, Yang X, Pei Z. Design and characterization of novel oxyntomodulin derivatives with potent dual GLP-1/glucagon receptor activation and prolonged antidiabetic effects. Life Sciences. 2020;253:117651.
44. Zhihong Y, Chen W, Qianqian Z, Lidan S, Qiang Z, Jing H, et al. Emerging roles of oxyntomodulin-based glucagon-like peptide-1/glucagon co-agonist analogs in diabetes and obesity. Peptides. 2023;162:170955.
45. Zhang M, Zhu L, Wu G, Zhang H, Wang X, Qi X. The impacts and mechanisms of dietary proteins on glucose homeostasis and food intake: A pivotal role of gut hormones. Critical Reviews in Food Science and Nutrition. 2024;64(33):12744-58.
46. Malik D, Narayanasamy N, Pratyusha VA, Thakur J, Sinha N. Digestion and assimilation of nutrients. InTextbook of nutritional biochemistry. Singapore: Springer Nature Singapore . 2023:79-111
47. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Towards personalized care: Unraveling the genomic and molecular basis of sepsis-induced respiratory complications. Archives of Clinical Toxicology. 2024;6(1):4-15.
48. Addissouky TA, Sayed IE, Ali MM, Wang Y. Emerging biomarkers for precision diagnosis and personalized treatment of cystic fibrosis. Journal of Rare Diseases. 2024;3(1):28.
49. Alicic RZ, Neumiller JJ. Incretin therapies for patients with type 2 diabetes and chronic kidney disease. Journal of Clinical Medicine. 2023;13(1):201.
50. Andreasen CR, Andersen A, Vilsbøll T. The future of incretins in the treatment of obesity and non-

[DOI: 10.18502/ijdo.v17i2.18851]

alcoholic fatty liver disease. Diabetologia. 2023;66(10):1846-58.
51. Camilleri M, Acosta A. Newer pharmacological interventions directed at gut hormones for obesity. British Journal of Pharmacology. 2024;181(8):1153-64.
52. Tschöp M, Nogueiras R, Ahrén B. Gut hormone-based pharmacology: novel formulations and future possibilities for metabolic disease therapy. Diabetologia. 2023;66(10):1796-808.
53. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Recent developments in the diagnosis, treatment, and management of cardiovascular diseases through artificial intelligence and other innovative approaches. Journal of Biomed Research. 2024;5(1):29-40.
54. Addissouky TA, El Sayed IE, Ali MM, Wang Y, El Baz A, Elarabany N, et al. Shaping the future of cardiac wellness: exploring revolutionary approaches in disease management and prevention. Journal of Clinical Cardiology. 2024;5(1):6-29.
55. Lyons SA, Beaudry JL. Synergistic combinations of gut-and pancreas-hormone-based therapies: advancements in treatments for metabolic diseases. Endocrinology. 2023;164(11):bqad153.
56. Beloqui A. Gut hormone stimulation as a therapeutic approach in oral peptide delivery. Journal of Controlled Release. 2024;373:31-7.
57. Kukova L, Munir KM, Sayeed A, Davis SN. Assessing the therapeutic and toxicological profile of novel GLP-1 receptor agonists for type 2 diabetes. Expert Opinion on Drug Metabolism & Toxicology. 2024;20(10):939-52.
58. Kaplan JM, Zaman A, Abushamat LA. Curbing the Obesity Epidemic: Should GLP-1 Receptor Agonists Be the Standard of Care for Obesity?. Current Cardiology Reports. 2024;26(9):1011-9.
59. Wardeh R, Iswadi TH, Alsharayri H, Rashid F, Alhashemi N, Bashier A. Dual GLP-1/GIP agonist tirzepatide for diabetes and obesity: a review of the evidence. Journal of Diabetes and Endocrine Practice. 2024;7(01):15-24.
60. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Transforming glomerulonephritis care through emerging diagnostics and therapeutics. Journal of Biomed Research. 2024;5(1):41-52.
61. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Precision medicine and immunotherapy advances transforming colorectal cancer treatment. Journal of Cancer Biology. 2024;5(2):38-43.
62. Addissouky TA, El Sayed IE, Ali MM, Alubiady MH, Wang Y. Harnessing innovation for the future of breast cancer management. Clinical Research in Oncology. 2024;1(1):10-7.
63. Ansari S, Khoo B, Tan T. Targeting the incretin system in obesity and type 2 diabetes mellitus. Nature Reviews Endocrinology. 2024;20(8):447-59.
64. Ali A, Flatt PR, Irwin N. Gut-Derived Peptide Hormone Analogues and Potential Treatment of Bone Disorders in Obesity and Diabetes Mellitus. Clinical Medicine Insights: Endocrinology and Diabetes. 2024:11795514241238059.
65. Mengoli M, Conti G, Fabbrini M, Candela M, Brigidi P, Turroni S, et al. Microbiota-gut-brain axis and ketogenic diet: how close are we to tackling epilepsy?. Microbiome Research Reports. 2023;2(4):32.
66. Leigh SJ, Lynch CM, Bird BR, Griffin BT, Cryan JF, Clarke G. Gut microbiota-drug interactions in cancer pharmacotherapies: implications for efficacy and adverse effects. Expert Opinion on Drug Metabolism & Toxicology. 2022;18(1):5-26.
67. Addissouky TA, Wang Y, El Tantawy El Sayed I, Majeed MA, Khalil AA. Emerging technologies and advanced biomarkers for enhanced toxicity prediction and safety pharmacology. Advances in Clinical Toxicology. 2024;9(1):293.
68. Addissouky TA, Wang Y, El Tantawy El Sayed I, Majeed MA, Khalil AA. Transforming toxicity assessment through microphysiology, bioprinting, and computational modeling. Advances in Clinical Toxicology. 2024;9(1):295.
69. Mehrotra N, Kharbanda S, Singh H. Peptide-based combination nanoformulations for cancer therapy. Nanomedicine. 2020;15(22):2201-17.
70. Finan B, Parlee SD, Yang B. Nuclear hormone and peptide hormone therapeutics for NAFLD and NASH. Molecular Metabolism. 2021;46:101153.
71. Addissouky TA, El Sayed IE, Ali MM. Regenerating damaged joints: the promise of tissue engineering and nanomedicine in lupus arthritis. J Clinical Orthopaedics and Trauma Care. 2024;6(2):2694-0248.
72. Addissouky TA, El Sayed IE, Ali MM. Conservative and emerging rehabilitative approaches for knee osteoarthritis management. J Clinical Orthopaedics and Trauma Care. 2024;6(2):2694-0248.
73. Xu L, Yuan Y, Che Z, Tan X, Wu B, Wang C, Xu C, Xiao J. The hepatoprotective and hepatotoxic roles of sex and sex-related hormones. Frontiers in Immunology. 2022;13:939631.
74. Firman C, Batterham RL. A new era in gut hormone-based pharmacotherapy for people with obesity. Proceedings of the Nutrition Society. 2022;81(3):217-26.
75. Olanrewaju OA, Sheeba F, Kumar A, Ahmad S, Blank N, Kumari R, et al. Novel therapies in diabetes: a comprehensive narrative review of GLP-1 receptor agonists, SGLT2 inhibitors, and beyond. Cureus. 2023;15(12):e51151.
76. Patel D, Smith A. Patient initiation and maintenance of GLP-1 RAs for treatment of

[DOI: 10.18502/ijdo.v17i2.18851]

obesity. Expert Review of Clinical Pharmacology. 2021;14(10):1193-204.
77. Wal P, Aziz N, Prajapati H, Soni S, Wal A. Current Landscape of Various Techniques and Methods of Gene Therapy through CRISPR Cas9 along with its Pharmacological and Interventional Therapies in the Treatment of Type 2 Diabetes Mellitus. Current Diabetes Reviews. 2024;20(6):110-27.
78. Meng H, Nan M, Li Y, Ding Y, Yin Y, Zhang M. Application of CRISPR-Cas9 gene editing technology in basic research, diagnosis and treatment of colon cancer. Frontiers in Endocrinology. 2023;14:1148412.
79. Addissouky TA, Wang Y, Megahed FA, El Agroudy AE, El Sayed IE, El-Torgoman AM. Novel biomarkers assist in detection of liver fibrosis in HCV patients. Egyptian Liver Journal. 2021;11:1-5.
80. Addissouky TA, El Agroudy AE, El-Torgoman AM, El Sayed IE, Ibrahim EM. Efficiency of alternative markers to assess liver fibrosis levels in viral hepatitis B patients. Biomedical Research. 2019;30(2):1-6.
81. Gigliotti G, Joshi R, Khalid A, Widmer D, Boccellino M, Viggiano D. Epigenetics, Microbiome and Personalized Medicine: Focus on Kidney Disease. International Journal of Molecular Sciences. 2024;25(16):8592.
82. Wang RC, Wang Z. Precision medicine: disease subtyping and tailored treatment. Cancers. 2023;15(15):3837.
83. Addissouky TA, Ayman E. El-Agroudy, Abdel Moneim AK El-Torgoman , Ibrahim E. El-Sayed.Efficacy of biomarkers in detecting fibrosis levels of liver diseases. World Journal of Medical Sciences. 2019;16(1):11-8.
84. Addissouky T. Detecting liver fibrosis by recent reliable biomarkers in viral hepatitis patients. American Journal of Clinical Pathology. 2019;152(1):S85.
85. Ahmed Z, Mohamed K, Zeeshan S, Dong X. Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. Database. 2020;2020:baaa010.
86. Alowais SA, Alghamdi SS, Alsuhebany N, Alqahtani T, Alshaya AI, Almohareb SN, et al. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC medical education. 2023;23(1):689.

[DOI: 10.18502/ijdo.v17i2.18851]