ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

G PROTEIN-COUPLED RECEPTORS (GPCRS): SIGNALING DIVERSITY AND THERAPEUTIC IMPLICATIONS

Jagat Pal Yadav[*1], Shubhrat Maheshwari[2], Ajeet Kumar[3], Alka[4], Ravi Kumar[5], Abhishek Mishra[6], Shailendra Singh Bhadauriya[6], Somesh Shukla[6], Neeraj Jain[7]

[1]Department of Pharmacology, Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, Uttar Pradesh 228118, India

[2]Rajarshi Rananjay Sinh College of Pharmacy, Amethi, Uttar Pradesh 227405, India.

[3]Faculty of Pharmacy, Future Institute of Medical Sciences, Bareilly, Uttar Pradesh, India.

[4]Amity Institute of Pharmacy, Amity University, Lucknow campus, Uttar Pradesh, India

[5]Narayan institute of pharmacy, Gopal Narayan Singh University, Jamuhar, Sasaram, Bihar-821305

[6]Faculty of Pharmaceutical Sciences, Rama University, Kanpur, 209217, India

[7]Teerthankar Mahaveer College of Pharmacy, TMU, Moradabad U.P, India

Corresponding Author

Jagat Pal Yadav*

Department of Pharmacology, Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, Uttar Pradesh 228118, India

Email: j.p.yaduvansi@gmail.com

Abstract:

G Protein-Coupled Receptors (GPCRs) constitute a large and diverse family of cell surface receptors that play a crucial role in transducing extracellular signals into intracellular responses. This manuscript aims to provide a comprehensive overview of GPCRs, exploring their structure, signaling pathways, physiological functions, and their significance as therapeutic targets. Understanding the intricate mechanisms underlying GPCR signaling is essential for the development of novel pharmacological interventions in various diseases.

Keywords: GPCRs, Signaling, protein kinase, arrestins.

1. Introduction

G Protein-Coupled Receptors (GPCRs) represent a fascinating and immensely diverse family of cell surface receptors that play a fundamental role in transducing extracellular signals into intracellular responses [1]. This group of receptors, also known as seven-transmembrane receptors, holds paramount importance in cellular communication and serves as a critical interface between the external environment and the intracellular machinery [2]. With their ability to sense an array of signaling molecules, ranging from neurotransmitters and hormones to photons, GPCRs regulate an extensive spectrum of physiological processes, making them central

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

players in human health and disease [3]. The discovery of GPCRs can be traced back to the pioneering work of Sir Alfred G. Gilman and Martin Rodbell, who were awarded the Nobel Prize in Physiology or Medicine in 1994 for their elucidation of G protein signaling pathways [4]. This breakthrough provided the foundation for understanding how cells interpret extracellular signals and paved the way for a deeper exploration of the vast GPCR family [5]. GPCRs share a common structural motif characterized by seven transmembrane alpha-helices connected by extracellular and intracellular loops. Despite this conserved structure, GPCRs exhibit remarkable diversity in their amino acid sequences, allowing them to recognize an extensive repertoire of ligands. This structural versatility is a testament to the adaptability of GPCRs in mediating a wide array of biological responses [6]. The functional significance of GPCRs is underscored by their involvement in a myriad of physiological processes [7]. From sensory perception (as seen in vision, taste, and olfaction) to the regulation of cardiovascular functions and neurotransmission in the nervous system, GPCRs are integral components of cellular signaling cascades. The ability of these receptors to modulate diverse downstream pathways emphasizes their role as orchestrators of cellular responses. The pharmacological relevance of GPCRs cannot be overstated [8]. A substantial portion of therapeutic agents currently in use target GPCRs, underscoring their significance in drug discovery and development. As our understanding of GPCR structure and function deepens, novel therapeutic strategies are emerging, providing innovative approaches for the treatment of various diseases [9].

2. Structural Features of G Protein-Coupled Receptors (GPCRs)

G Protein-Coupled Receptors (GPCRs) are integral membrane proteins that play a pivotal role in signal transduction across the cell membrane. The structural features of GPCRs are highly conserved, providing a scaffold for their diverse functions. Understanding the architecture of GPCRs is essential for unraveling their mechanisms of action and holds significant implications for drug design targeting these receptors [10].

GPCRs possess a distinctive seven alpha-helical transmembrane domain architecture, also known as a seven-transmembrane bundle. These helices traverse the lipid bilayer and are connected by intracellular and extracellular loops. The extracellular loops connect the transmembrane helices on the extracellular side [11]. These loops are involved in ligand recognition and binding, contributing to the specificity of GPCR activation. Intracellular loops connect the transmembrane helices on the cytoplasmic side [12]. These loops play a crucial role in interacting with G proteins, arrestins, and other intracellular signaling partners. The N-terminal domain is located extracellularly and varies in length among different GPCRs [13]. It can influence ligand binding and receptor activation in certain subtypes. The C-terminal domain is positioned intracellularly and plays a role in GPCR desensitization, internalization, and interactions with downstream signaling molecules [14]. GPCRs typically contain an orthosteric binding site where endogenous ligands bind. Some GPCRs also have allosteric binding sites that modulate receptor activity without directly interacting with the orthosteric site [15]. The ligand-

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

binding pocket is crucial for the receptor's specificity in recognizing a diverse array of ligands, including neurotransmitters, hormones, and drugs. The intracellular loops and the C-terminal tail form a conserved binding site for G proteins [1]. Upon ligand binding, GPCRs undergo conformational changes that allow them to interact with and activate heterotrimeric G proteins. GPCRs undergo post-translational modifications, including phosphorylation and glycosylation [16]. Phosphorylation by kinases and interaction with arrestins contribute to receptor desensitization and internalization. GPCRs can form homodimers or heterodimers, influencing their function and signaling properties [17]. Dimerization is dynamic and can impact receptor trafficking and signaling specificity. GPCRs exist in multiple conformational states, including active and inactive states. Ligand binding induces conformational changes that are transmitted to the intracellular domain, leading to downstream signaling events [18].

3. Signaling Pathways of G Protein-Coupled Receptors (GPCRs)

G Protein-Coupled Receptors (GPCRs) are versatile signaling molecules that transmit extracellular signals to intracellular effectors, orchestrating a wide array of physiological responses. The activation of GPCRs initiates intricate signaling pathways, involving G proteins, second messengers, and downstream effectors. Understanding these signaling cascades is crucial for deciphering the diverse roles GPCRs play in cellular physiology and for developing targeted therapeutic interventions [10].

Upon ligand binding, GPCRs undergo conformational changes that enable them to interact with heterotrimeric G proteins consisting of α, β, and γ subunits. Ligand binding induces the exchange of GDP for GTP on the Gα subunit, leading to the dissociation of Gα from the Gβγ subunits. Both Gα and Gβγ subunits can modulate the activity of various intracellular effectors, such as adenylyl cyclase, phospholipase C, and ion channels. GPCRs can activate adenylyl cyclase, leading to the production of cyclic AMP (cAMP) [19]. cAMP, in turn, activates protein kinase A (PKA), influencing various cellular processes. GPCRs can activate phospholipase C (PLC), leading to the cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 releases calcium from intracellular stores, and DAG activates protein kinase C (PKC) [20]. GPCRs can undergo phosphorylation by G protein-coupled receptor kinases (GRKs), leading to the recruitment of arrestins. Arrestins block further G protein activation, promoting receptor desensitization. Arrestins facilitate the internalization of GPCRs, directing them to endosomal compartments where they can continue to signal through arrestin-mediated pathways. GPCRs can activate multiple signaling pathways simultaneously, leading to cross-talk and integration of signals [21]. This integration contributes to the complexity and specificity of cellular responses. The GPCR family is diverse, and different GPCRs can couple to different G protein subtypes. This diversity allows for a wide range of cellular responses to various extracellular stimuli [2,22] Some GPCRs exhibit biased signaling, where they preferentially activate specific signaling pathways over others [6,23].This phenomenon has implications for drug development, enabling the design of drugs with selective therapeutic effects. Understanding the intricacies of GPCR signaling pathways is essential for

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

deciphering the physiological roles of these receptors and exploiting them for therapeutic purposes [18,24] The dynamic nature of GPCR signaling, including desensitization, internalization, and cross-talk, adds layers of complexity to their functionality. In the subsequent sections, we will explore the physiological functions governed by GPCRs, shedding light on their indispensable roles in various tissues and organ systems [25].

4. Physiological Functions of G Protein-Coupled Receptors (GPCRs)

G Protein-Coupled Receptors (GPCRs) play a central role in mediating diverse physiological functions throughout the human body [26]. These receptors are involved in responding to an extensive array of signals, including neurotransmitters, hormones, and sensory stimuli. Understanding the physiological functions of GPCRs is crucial for appreciating their significance in maintaining homeostasis and for targeting them in therapeutic interventions [10,27]

Rhodopsin, a GPCR in rod cells of the retina, is crucial for the detection of light. Upon absorption of photons, rhodopsin undergoes conformational changes, initiating the visual signal transduction cascade [9,28]. GPCRs in olfactory and taste receptor cells respond to odorants and tastants, respectively. This diverse family of receptors allows us to perceive and distinguish a wide range of smells and tastes. GPCRs are integral to neurotransmission, responding to neurotransmitters such as dopamine, serotonin, and [29,30]. Modulation of neuronal excitability and synaptic transmission is vital for cognitive and motor functions. GPCRs also play a role in neuromodulation, influencing the overall activity of neural circuits [31]. They contribute to processes like long-term potentiation (LTP) and long-term depression (LTD), crucial for learning and memory. GPCRs in cardiac cells regulate heart rate and contractility. Adrenergic receptors, for example, respond to adrenaline and norepinephrine, modulating cardiac function. GPCRs in blood vessels influence vascular tone by regulating smooth muscle contraction or relaxation [13]. This control is vital for maintaining blood pressure and blood flow. GPCRs mediate the effects of numerous hormones, including those involved in the regulation of metabolism, growth, and reproductive functions [32]. Examples include receptors for insulin, glucagon, and thyroid hormones [33]. GPCRs in the hypothalamus and pituitary gland regulate the release of hormones that, in turn, control the adrenal gland's production of stress hormones like cortisol. GPCRs on immune cells respond to chemokines and cytokines, directing immune cell migration, activation, and communication [34,35] This regulation is crucial for an effective immune response. GPCRs in the gastrointestinal tract modulate smooth muscle contraction, influencing processes like peristalsis and gut motility. GPCRs on glandular cells in the digestive system regulate the secretion of digestive enzymes in response to food intake [36]. GPCRs in the kidneys play a role in regulating fluid and electrolyte balance by influencing processes like sodium reabsorption and water excretion. GPCRs can influence cell growth and proliferation by activating intracellular pathways involved in cell cycle progression [10,37]. GPCRs contribute to the differentiation of stem cells into specialized cell types during development and tissue repair. The multifaceted roles of GPCRs in various tissues and organ systems highlight their importance in maintaining physiological homeostasis [38]. Dysregulation of GPCR signaling is implicated in a variety of

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

diseases, making these receptors attractive targets for therapeutic interventions. In the following sections, we will explore the therapeutic implications of targeting GPCRs and the challenges associated with developing drugs that modulate their activities [14,39].

5. Therapeutic Implications

5.1 Drug Discovery Targeting G Protein-Coupled Receptors

G Protein-Coupled Receptors (GPCRs) have long been at the forefront of drug discovery efforts, serving as prominent targets for a diverse range of therapeutic interventions [40]. Their involvement in numerous physiological processes and their responsiveness to various ligands make them ideal candidates for drug development. The exploration of GPCRs as drug targets has led to the development of a multitude of pharmaceuticals that modulate GPCR activity, influencing cellular signaling and providing treatment options for a broad spectrum of diseases [41].

Most traditional drugs targeting GPCRs are orthosteric ligands that compete with endogenous ligands for binding to the receptor's active site. Examples include beta-blockers targeting adrenergic receptors. Allosteric modulators bind to sites distinct from the orthosteric site, modulating the receptor's activity [42]. This approach allows for more selective and fine-tuned control of GPCR function. Targeting adrenergic receptors, beta-blockers are used to treat conditions like hypertension and heart failure by reducing the effects of adrenaline. GPCRs, especially dopamine receptors, are targeted by antipsychotic drugs to manage conditions like schizophrenia and bipolar disorder [5,43]. H1 receptors, a type of GPCR, are targeted by anti-histamines to alleviate allergic reactions and symptoms. GPCRs, specifically opioid receptors, are the target for analgesics like morphine, providing pain relief [31]. Serotonin and norepinephrine receptors, both GPCRs, are targeted by antidepressant medications to manage mood disorders. Advances in understanding biased signaling allow for the development of ligands that selectively activate specific downstream pathways, providing more targeted therapeutic effects. Some ligands can activate one signaling pathway over another, leading to functionally selective modulation of GPCR activity [36]. High-resolution structures of GPCRs obtained through techniques like X-ray crystallography and cryo-electron microscopy enable rational drug design, facilitating the development of highly specific ligands. Computational methods, including molecular dynamics simulations and virtual screening, aid in predicting ligand-receptor interactions and optimizing drug candidates. Optogenetic techniques, where light-sensitive GPCRs are engineered into cells, allow for precise control of GPCR activation in specific tissues and cell types [15,44].

6. Future Perspectives

Advancements in understanding GPCR polymorphisms and individual variations may pave the way for personalized medicine, tailoring drug treatments to an individual's genetic makeup. Continued research into GPCR biology may reveal disease-specific alterations in GPCR signaling, leading to the development of highly targeted therapies. Innovative strategies, such as the use of gene therapies and RNA-based approaches, may open new avenues for GPCR-targeted

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

therapeutics. GPCRs continue to be pivotal targets for drug discovery, offering a vast landscape for developing medications that modulate cellular signaling. As our understanding of GPCR structure, function, and signaling pathways advances, so too will the sophistication of drug discovery efforts, leading to more precise and efficacious therapeutic interventions across a spectrum of diseases.

7. Conclusion

G Protein-Coupled Receptors stand at the crossroads of cellular signaling, influencing diverse physiological processes. A deeper understanding of GPCR structure and function provides valuable insights for drug discovery and therapeutic interventions, offering hope for improved treatments across a spectrum of diseases. Continued research into the complexities of GPCR signaling holds promise for the development of more precise and effective pharmacological interventions in the future.

References:

[1] D.B.J. Bone, J. Meister, J.R. Knudsen, D. Dattaroy, A. Cohen, R. Lee, H. Lu, D. Metzger, T.E. Jensen, J. Wess, Skeletal muscle–specific activation of Gq signaling maintains glucose homeostasis, Diabetes. 68 (2019) 1341–1352. https://doi.org/10.2337/db18-0796.

[2] C.P. Briscoe, A.J. Peat, S.C. McKeown, D.F. Corbett, A.S. Goetz, T.R. Littleton, D.C. McCoy, T.P. Kenakin, J.L. Andrews, C. Ammala, J.A. Fornwald, D.M. Ignar, S. Jenkinson, Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40: Identification of agonist and antagonist small molecules, Br. J. Pharmacol. 148 (2006) 619–628. https://doi.org/10.1038/sj.bjp.0706770.

[3] M. Rossi, L. Zhu, S.M. McMillin, S.P. Pydi, S. Jain, L. Wang, Y. Cui, R.J. Lee, A.H. Cohen, H. Kaneto, M.J. Birnbaum, Y. Ma, Y. Rotman, J. Liu, T.J. Cyphert, T. Finkel, O.P. McGuinness, J. Wess, Hepatic gi signaling regulates whole-body glucose homeostasis, J. Clin. Invest. 128 (2018) 746–759. https://doi.org/10.1172/JCI94505.

[4] S. Auguste, A. Fisette, M.F. Fernandes, C. Hryhorczuk, V. Poitout, T. Alquier, S. Fulton, Central Agonism of GPR120 Acutely Inhibits Food Intake and Food Reward and Chronically Suppresses Anxiety-Like Behavior in Mice, Int. J. Neuropsychopharmacol. 19 (2016) 1–10. https://doi.org/10.1093/ijnp/pyw014.

[5] I. Kimura, A. Ichimura, R. Ohue-Kitano, M. Igarashi, Free fatty acid receptors in health and disease, Physiol. Rev. 100 (2020) 171–210. https://doi.org/10.1152/physrev.00041.2018.

[6] S. Amisten, I.M. Al-Amily, A. Soni, R. Hawkes, P. Atanes, S.J. Persaud, P. Rorsman, A. Salehi, Anti-diabetic action of all-trans retinoic acid and the orphan G protein coupled receptor GPRC5C in pancreatic β-cells, Endocr. J. 64 (2017) 325–338. https://doi.org/10.1507/endocrj.EJ16-0338.

[7] S. Jain, S.P. Pydi, K.S. Toti, B. Robaye, M. Idzko, O. Gavrilova, J. Wess, K.A. Jacobson, Lack of adipocyte purinergic P2Y6 receptor greatly improves whole body glucose homeostasis, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 30763–30774.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

https://doi.org/10.1073/pnas.2006578117.

[8] K.T. Weiß, M. Fante, G. Köhl, J. Schreml, F. Haubner, M. Kreutz, S. Haverkampf, M. Berneburg, S. Schreml, Proton-sensing G protein-coupled receptors as regulators of cell proliferation and migration during tumor growth and wound healing, Exp. Dermatol. 26 (2017) 127–132. https://doi.org/10.1111/exd.13209.

[9] P. Dunér, I. Mohammad Al-Amily, A. Soni, O. Asplund, F. Safi, P. Storm, L. Groop, S. Amisten, A. Salehi, Adhesion G protein-coupled receptor G1 (ADGRG1/GPR56) and pancreatic β-cell function, J. Clin. Endocrinol. Metab. 101 (2016) 4637–4645. https://doi.org/10.1210/jc.2016-1884.

[10] S. Amisten, P. Atanes, R. Hawkes, I. Ruz-Maldonado, B. Liu, F. Parandeh, M. Zhao, G.C. Huang, A. Salehi, S.J. Persaud, A comparative analysis of human and mouse islet G-protein coupled receptor expression, Sci. Rep. 7 (2017) 1–11. https://doi.org/10.1038/srep46600.

[11] J.P. Yadav, D.K. Patel, P. Pathak, M. Grishina, Role of G-protein coupled receptor (GPCRs)/(GPR-120) as an agonists in diabetic wound healing, Obes. Med. 36 (2022) 100466. https://doi.org/10.1016/j.obmed.2022.100466.

[12] A. Jabeen, S. Ranganathan, Applications of machine learning in GPCR bioactive ligand discovery, Curr. Opin. Struct. Biol. 55 (2019) 66–76.

[13] B.K. Kobilka, X. Deupi, Conformational complexity of G-protein-coupled receptors, Trends Pharmacol. Sci. 28 (2007) 397–406. https://doi.org/10.1016/j.tips.2007.06.003.

[14] X. Zhang, M.J. Macielag, GPR120 agonists for the treatment of diabetes: a patent review (2014 present), Expert Opin. Ther. Pat. 30 (2020) 729–742. https://doi.org/10.1080/13543776.2020.1811852.

[15] H.J. Ting, J.P. Murad, E.V.P. Espinosa, F.T. Khasawneh, Thromboxane A2 receptor: Biology and function of a peculiar receptor that remains resistant for therapeutic targeting, J. Cardiovasc. Pharmacol. Ther. 17 (2012) 248–259. https://doi.org/10.1177/1074248411424145.

[16] L. Wang, L. Zhu, J. Meister, D.B.J. Bone, S.P. Pydi, M. Rossi, J. Wess, Use of DREADD Technology to Identify Novel Targets for Antidiabetic Drugs, Annu. Rev. Pharmacol. Toxicol. 61 (2021) 421–440. https://doi.org/10.1146/annurev-pharmtox-030220-121042.

[17] K. Ahmed, S. Tunaru, S. Offermanns, GPR109A, GPR109B and GPR81, a family of hydroxy-carboxylic acid receptors, Trends Pharmacol. Sci. 30 (2009) 557–562. https://doi.org/10.1016/j.tips.2009.09.001.

[18] G. Milligan, B. Shimpukade, T. Ulven, B.D. Hudson, Complex pharmacology of free fatty acid receptors, Chem. Rev. 117 (2017) 67–110. https://doi.org/10.1021/acs.chemrev.6b00056.

[19] N. Tuteja, Signaling through G protein coupled receptors, Plant Signal. Behav. 4 (2009) 942–947. https://doi.org/10.4161/psb.4.10.9530.

[20] C. Draper-joyce, S. George, B. Furness, Conformational Transitions and the Activation of

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

Heterotrimeric G Proteins by G Protein-Coupled Receptors, ACS Pharmacol. Transl. Sci. (2019) 285–290. https://doi.org/10.1021/acsptsci.9b00054.

[21] Z. Bologna, J.P. Teoh, A.S. Bayoumi, Y. Tang, I.M. Kim, Biased g protein-coupled receptor signaling: New player in modulating physiology and pathology, Biomol. Ther. 25 (2017) 12–25. https://doi.org/10.4062/biomolther.2016.165.

[22] J.F.M. Post, R.S. Varma, Growth inhibitory effects of bioflavonoids and related compounds on human leukemic CEM-C1 and CEM-C7 cells, Cancer Lett. 67 (1992) 207–213.

[23] Y.H. Lee, J.J. Chang, M.C. Yang, C.T. Chien, W.F. Lai, Acceleration of wound healing in diabetic rats by layered hydrogel dressing, Carbohydr. Polym. 88 (2012) 809–819. https://doi.org/10.1016/j.carbpol.2011.12.045.

[24] J. Khan, S. Saraf, S. Saraf, Preparation and evaluation of luteolin-phospholipid complex as an effective drug delivery tool against GalN/LPS induced liver damage, Pharm. Dev. Technol. 21 (2016) 475–486. https://doi.org/10.3109/10837450.2015.1022786.

[25] F. Reimann, F.M. Gribble, G protein-coupled receptors as new therapeutic targets for type 2 diabetes, Diabetologia. 59 (2016) 229–233. https://doi.org/10.1007/s00125-015-3825-z.

[26] S. Sano, S. Itami, K. Takeda, M. Tarutani, Y. Yamaguchi, H. Miura, K. Yoshikawa, S. Akira, J. Takeda, Keratinocyte-specific ablation of Stat3 exhibits impaired skin remodeling, but does not affect skin morphogenesis, EMBO J. 18 (1999) 4657–68. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1171539&tool=pmcentrez&rendertype=abstract.

[27] M. Valko, C.J. Rhodes, J. Moncol, M. Izakovic, M. Mazur, Free radicals , metals and antioxidants in oxidative stress-induced cancer, 160 (2006) 1–40. https://doi.org/10.1016/j.cbi.2005.12.009.

[28] B.A. Lipsky, J. Aragón-Sánchez, M. Diggle, J. Embil, S. Kono, L. Lavery, É. Senneville, V. Urbančič-Rovan, S. Van Asten, IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes, Diabetes. Metab. Res. Rev. 32 (2016) 45–74. https://doi.org/10.1002/dmrr.2699.

[29] E. Yadav, D. Singh, P. Yadav, A. Verma, L.J. Mcgaw, Comparative Evaluation of Prosopis cineraria (L .) Druce and Its ZnO Nanoparticles on Scopolamine Induced Amnesia, 9 (2018) 1–18. https://doi.org/10.3389/fphar.2018.00549.

[30] B. Petersen, I. Vesper, B. Pachwald, N. Dagenbach, S. Buck, D. Waldenmaier, L. Heinemann, Diabetes management intervention studies: lessons learned from two studies, Trials. 22 (2021) 1–9. https://doi.org/10.1186/s13063-020-05017-3.

[31] R. Berra-Romani, P. Faris, G. Pellavio, M. Orgiu, S. Negri, G. Forcaia, V. Var---gaz-Guadarrama, M. Garcia-Carrasco, L. Botta, G. Sancini, U. Laforenza, F. Moccia, Histamine induces intracellular Ca2+ oscillations and nitric oxide release in endothelial cells from brain microvascular circulation, J. Cell. Physiol. 235 (2020) 1515–1530. https://doi.org/10.1002/jcp.29071.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

[32] P. Fomby, A.J. Cherlin, A. Hadjizadeh, C.J. Doillon, V. Sueblinvong, D.J. Weiss, J.H.T. Bates, T. Gilbert, W.C. Liles, C. Lutzko, J. Rajagopal, D.J. Prockop, D. Chambers, A. Giangreco, A. Keating, D. Kotton, P.I. Lelkes, D.E. Wagner, D.J. Prockop, Stem cells and cell therapies in lung biology and diseases: Conference report, Ann. Am. Thorac. Soc. 12 (2010) 181–204. https://doi.org/10.1002/term.

[33] I. Iakovleva, A. Begum, M. Pokrzywa, M. Walfridsson, A.E. Sauer-Eriksson, A. Olofsson, The flavonoid luteolin, but not luteolin-7-O-glucoside, prevents a transthyretin mediated toxic response., PLoS One. 10 (2015) e0128222. https://doi.org/10.1371/journal.pone.0128222.

[34] W.N. Hozzein, G. Badr, B.M. Badr, A. Allam, A. Al Ghamdi, M.A. Al-Wadaan, N.S. Al-Waili, Bee venom improves diabetic wound healing by protecting functional macrophages from apoptosis and enhancing Nrf2, Ang-1 and Tie-2 signaling, Mol. Immunol. 103 (2018) 322–335. https://doi.org/10.1016/j.molimm.2018.10.016.

[35] D. Li, H. Peng, L. Qu, P. Sommar, A. Wang, T. Chu, X. Li, X. Bi, Q. Liu, I. Gallais Sérézal, O. Rollman, W. Lohcharoenkal, X. Zheng, S. Eliasson Angelstig, J. Grünler, A. Pivarcsi, E. Sonkoly, S.B. Catrina, C. Xiao, M. Ståhle, Q.S. Mi, L. Zhou, N. Xu Landén, miR-19a/b and miR-20a Promote Wound Healing by Regulating the Inflammatory Response of Keratinocytes, J. Invest. Dermatol. 141 (2021) 659–671. https://doi.org/10.1016/j.jid.2020.06.037.

[36] M.M. Hopkins, Z. Zhang, Z. Liu, K.E. Meier, Eicosopentaneoic acid and other free fatty acid receptor agonists inhibit lysophosphatidic acidand epidermal growth factor-induced proliferation of human breast cancer cells, J. Clin. Med. 5 (2016) 1–14. https://doi.org/10.3390/jcm5020016.

[37] M. Petkovic, A.E. Sørensen, E.C. Leal, E. Carvalho, L.T. Dalgaard, Mechanistic Actions of microRNAs in Diabetic Wound Healing, Cells. 9 (2020). https://doi.org/10.3390/cells9102228.

[38] L.B. Pucar, Diabetes, Dipeptidyl Peptidase iv and Wound Healing: from Basic Science to Therapeutic Possibilities, Open Access J. Biomed. Eng. Biosci. 2 (2018) 230–236. https://doi.org/10.32474/oajbeb.2018.02.000147.

[39] Y. Wang, M. Chen, J. Zhang, X.-L. Zhang, X.-J. Huang, X. Wu, Q.-W. Zhang, Y.-L. Li, W.-C. Ye, Flavone C-glycosides from the leaves of Lophatherum gracile and their in vitro antiviral activity., Planta Med. 78 (2012) 46–51. https://doi.org/10.1055/s-0031-1280128.

[40] J.A. Salon, D.T. Lodowski, K. Palczewski, The Significance of G Protein-Coupled Receptor, 63 (2011) 901–937. https://doi.org/10.1124/pr.110.003350.901.

[41] V. V Gurevich, E. V Gurevich, GPCR Signaling Regulation : The Role of GRKs and Arrestins, 10 (2019) 1–11. https://doi.org/10.3389/fphar.2019.00125.

[42] A.S. Hauser, M.M. Attwood, M. Rask-Andersen, H.B. Schiöth, D.E. Gloriam, Trends in GPCR drug discovery: New agents, targets and indications, Nat. Rev. Drug Discov. 16 (2017) 829–842. https://doi.org/10.1038/nrd.2017.178.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 09, 2022

[43] A.N. Anbazhagan, S. Priyamvada, T. Gujral, S. Bhattacharyya, W.A. Alrefai, P.K. Dudeja, A. Borthakur, A novel anti-inflammatory role of GPR120 in intestinal epithelial cells, Am. J. Physiol. - Cell Physiol. 310 (2016) C612–C621. https://doi.org/10.1152/ajpcell.00123.2015.

[44] M. Parvathaneni, A.K. Awol, M. Kumari, K. Lan, M. Lingam, Application of Artificial Intelligence and Machine Learning in Drug Discovery and Development, J. Drug Deliv. Ther. 13 (2023) 151–158. https://doi.org/10.22270/jddt.v13i1.5867.