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Editorial

Drug Discovery

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More than 50% of deaths worldwide are linked to chronic inflammatory disorders, including cancer, cardiovascular disease, dementia, stroke, and diabetes. This makes inflammation one of the most prevalent target processes and reactions in the human body [1,2]. A tissue injury triggers the body's inflammatory response, which leads to inflammatory diseases. Acute inflammation that is not regulated leads to chronic inflammation, which increases the risk of cancer, neurological disorders, and autoimmune diseases in the body [3,4]. The development of gastrointestinal illnesses is strongly influenced by the gut microbiota [5,6]. The link between the gut microbiota and health is becoming increasingly obvious. The diversity and quantity of microbiota is crucial and essential for human welfare. Age, stress, antibiotic use, poor nutrition, and other factors can cause dysbiosis, i.e., imbalance, which can lead to inflammation and the progression of chronic diseases. Chronic inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are caused by gut dysbiosis [6,7].

Many signaling substances that are involved in the intricate pathophysiological process of inflammation are released by leucocytes, macrophages, and mast cells as they go through various biological responses. Examples of these include the production of inflammatory mediators like nitric oxide, prostaglandin (PG, PGE2), and tumor necrosis factor (TNF-), as well as phagocytic uptake [8,9]. These elements contribute to the extravasation of fluids and proteins, and leucocyte accumulation at the inflammatory site, which causes edema to develop [10]. It is also generally acknowledged that cytokines, which are produced by the immune system or central nervous system cells, may directly sensitize the peripheral nociceptors [11].

Bradykinins, TNF, and interleukins (ILs), as well as PGs, all affect how well free nerve terminals can transduce signals, which results in hyperalgesia and pain. The pyrogens that an infection creates, such as ILs, TNF-, and interferon, are what drive the hypothalamus to produce PGE2 and boost its internal temperature, which is what causes a fever. Inflammation is followed by a fever or pyrexia [12]. Increased prostaglandin synthesis has been associated with fever, discomfort, and inflammation [13]. As a result, analgesic and antipyretic characteristics are anticipated in the majority of anti-inflammatory medications [14,15]. Inflammation is also related to cancer; the growth and proliferation of tumors are significantly influenced by inflammation.

To relieve pain, fever, and inflammation, while also protecting the cardiovascular system, non-steroidal anti-inflammatory drugs are used. However, the side effects of currently available anti-inflammatory medications, which include gastric ulcers, renal damage, bronchospasms, and cardiac problems, have limited their usage [16,17]. Due to the adverse effects of non-steroidal anti-inflammatory drugs and opioids, there is a high demand for new drugs with fewer or no side effects. Finding novel drugs takes years of effort and funding, as well as a lot of hard work.

Over the past 100 years, pharmaceutical industry-discovered drugs have had a significant impact on many facets of our culture and the practice of medicine. For many years, the method of drug development relied on ethnobotanical expertise and was target- and mechanism-agnostic.

The process of finding new drugs usually includes identifying targets and creating effective pharmacological molecules to target them. Despite decades of experimental

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research in this field, around 96% of medication development projects fail. Likewise, the pharmaceutical business experiences a great deal of pressure due to the high attrition rate of drug candidates during the drug discovery process.

It has always been an important scientific topic to investigate the biological activities of newly synthesized compounds. This is connected to the never-ending interest in drug discovery or in finding a molecule with certain "useful" properties that can affect a function or process in the human body. Selecting the most promising targets from the huge pool of diverse potential candidates is one of the major difficulties of the post-genome era [18]. The choice of "the right" biological target may be the most crucial one made in pharmacological research and development [19]. This group includes biotherapeutics as well as small molecules.

Computational technologies and big data are becoming effective in predicting biological target drug ability and the drug-likeness of new therapeutic agents, as experimental research approaches become less common [20]. The multiple stages that must be completed between the decision to choose a target and the start of clinical trials to prove efficacy in humans typically follow a clear-cut pattern. After screening and hit identification, optimization rounds based on pharmacological and toxicological testing are conducted, and then pharmaceutical development and production take place.

There are a number of limitations to the systematic use of experiments in the drug discovery process. A few of these elements are the frequency of the newly synthesized compounds, the quantitative restrictions of tissue samples, and the need to restrict animal testing. In this situation, it is conceivable to presume that in silico computer models, which are both an excellent supplement and a practical replacement for biological investigations, may be used to replace biological investigations [21–23]. A drug candidate needs to reach its pharmacological target within the body, reach the right concentration at the site of action, and stay there long enough to be utilized as a medicine. Due to their poor pharmacokinetics and bioavailability, many promising biologically active compounds that are intended for use as medications fail. In silico research has made it possible to identify new drugs through target identification and validation, contributing to ongoing advancements in the drug discovery and development process. Several methods are employed to assess possible compounds with drug-like characteristics, including quantitative structure–activity and structure–property relationship models and in silico screening, which calculate anticipated biological effects, solubility, sufficient oral bioavailability, synthetic accessibility, intestinal absorption, and blood–brain barrier penetration [24–27].

Established through analyses of the physiochemical or structural characteristics of small-scale organic drugs or drug candidates, the concept of drug-likeness has been widely used to screen out compounds with undesirable properties, particularly those with poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles [23,28–33]. With varying goals, new computational algorithms and analytical techniques are being created as the volume of biological data continues to increase. This field covers a broad range of topics, including medication toxicity prediction and protein structure prediction. The majority of semi-empirical force-field- and quantum-mechanics-based molecular modeling methods demonstrate proven accuracy in analyzing small structural datasets, while statistics-based methods like machine learning, QSAR, and other specialized data analytics methods are robust for large-scale data analysis [34].

As a conclusion, modern drug discovery methodologies and technologies have had a significant impact on the increasing number of first-in-class pharmaceuticals approved in recent years, in line with the pharmaceutical industry's drive to find breakthrough therapies [35,36].

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References

1. Eming, S.A.; Krieg, T.; Davidson, J.M. Inflammation in wound repair: Molecular and cellular mechanisms. *J. Investig. Dermatol.* **2007**, *127*, 514–525. [CrossRef] [PubMed]
2. Burayk, S.; Oh-Hashi, K.; Kandeel, M. Drug Discovery of New Anti-Inflammatory Compounds by Targeting Cyclooxygenases. *Pharmaceuticals* **2022**, *15*, 282. [CrossRef] [PubMed]
3. Ejaz Ahmed, M.; Khan, M.M.; Javed, H.; Vaibhav, K.; Khan, A.; Tabassum, R.; Ashafaq, M.; Islam, F.; Safhi, M.M.; Islam, F. Amelioration of Cognitive Impairment and Neurodegeneration by Catechin Hydrate in Rat Model of Streptozotocin-Induced Experimental Dementia of Alzheimer's Type. *Neurochem. Int.* **2013**, *62*, 492–501. [CrossRef] [PubMed]
4. Kodydkova, J.; Vavrova, L.; Stankova, B.; Macasek, J.; Krechler, T.; Zak, A. Antioxidant Status and Oxidative Stress Markers in Pancreatic Cancer and Chronic Pancreatitis. *Pancreas* **2013**, *42*, 614–621. [CrossRef]
5. Valdes, A.; Walter, J.; Segal, E.; Spector, T.D. Role of the gut microbiota in nutrition and health. *BMJ* **2018**, *361*, k2179. [CrossRef] [PubMed]
6. Mitropoulou, G.; Stavropoulou, E.; Vaou, N.; Tsakris, Z.; Voidarou, C.; Tsiotsias, A.; Tsigalou, C.; Taban, B.M.; Kourkoutas, Y.; Bezirtzoglou, E. Insights into Antimicrobial and Anti-Inflammatory Applications of Plant Bioactive Compounds. *Microorganisms* **2023**, *11*, 1156. [CrossRef]
7. Bürger, M.; Lange, K.; Stallmach, A. Intestinales Mikrobiom und chronisch-entzündliche Darmerkrankungen: Feindschaft oder Freundschaft? *Gastroenterologe* **2015**, *10*, 87–101. [CrossRef]
8. Kinne, R.W.; Brauer, R.; Stuhlmuller, B.; Palombo-Kinne, E.; Burmester, G.R. Macrophages in rheumatoid arthritis. *Arthritis Res.* **2000**, *2*, 189–202. [CrossRef]
9. Yu, T.; Lee, J.; Lee, Y.G.; Byeon, S.E.; Kim, M.H.; Sohn, E.H.; Lee, Y.J.; Lee, S.G.; Cho, J.Y. In vitro and in vivo antiinflammatory effects of ethanol extract from *Acer tegmentosum*. *J. Ethnopharmacol.* **2010**, *128*, 139–147. [CrossRef]
10. White, M. Mediators of inflammation and inflammatory process. *J. Allergy Clin. Immunol.* **1999**, *103*, S378–S381. [CrossRef]
11. Obreja, O.; Rathee, P.K.; Lips, K.S.; Distler, C.; Kress, M. IL-1 beta potentiates heat activated currents in rat sensory neurons: Involvement of IL-1RI, tyrosine kinase, and protein kinase C. *FASEB J.* **2002**, *16*, 1497–1503. [CrossRef] [PubMed]
12. Khan, A.; Baki, M.A.; Al-Bari, M.A.A.; Hasan, S.; Mosaddik, M.A.; Rahman, M.M.; Haque, M.E. Antipyretic activity of roots of *Laportea crenulata* Gaud in rabbit. *RJMMS* **2007**, *2*, 58–61.
13. Rang, H.P.; Dale, M.; Ritter, J. *Pharmacology*, 4th ed.; Churchill Livingstone: New York, NY, USA, 2001.
14. Dewanjee, S.; Maiti, A.; Sahu, R.; Dua, T.K.; Mandal, S.C. Study of anti-inflammatory and antinociceptive activity of hydroalcoholic extract of *Schima wallichii* bark. *Pharm. Biol.* **2009**, *47*, 402–440. [CrossRef]
15. Sengar, N.; Joshi, A.; Prasad, S.K.; Hemalatha, S. Anti-inflammatory, analgesic and anti-pyretic activities of standardized root extract of *Jasminum sambac*. *J. Ethnopharmacol.* **2015**, *160*, 140–148. [CrossRef] [PubMed]
16. Burke, A.; Smyth, E.; Fitzgerald, G.A. Analgesic-antipyretic agents: Pharmacotherapy of gout. In *Goodman and Gilmans the Pharmacological Basis of Therapeutics*; Brunton, L.L., Lazo, J.S., Parker, K.L., Eds.; McGraw Hill: New York, NY, USA, 2006.
17. Shah, A.S.; Alagawadi, K.R. Anti-inflammatory, analgesic and antipyretic properties of *Thespesia populnea* Soland ex. Correa seed extracts and its fractions in animal models. *J. Ethnopharmacol.* **2011**, *137*, 1504–1509. [CrossRef]
18. Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* **2017**, *7*, 42717. [CrossRef]
19. Liao, J.; Wang, Q.; Wu, F.; Huang, Z. In Silico Methods for Identification of Potential Active Sites of Therapeutic Targets. *Molecules* **2022**, *27*, 7103. [CrossRef]
20. Agoni, C.; Olotu, F.A.; Ramharack, P.; Soliman, M.E. Druggability and drug-likeness concepts in drug design: Are biomodelling and predictive tools having their say? *J. Mol. Model.* **2020**, *26*, 120. [CrossRef]
21. Ekins, S.; Olechno, J.; Williams, A.J. Dispensing Processes Impact Apparent Biological Activity as Determined by Computational and Statistical Analyses. *PLoS ONE* **2013**, *8*, e62325. [CrossRef] [PubMed]
22. Roughley, S.D.; Jordan, A.M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. [CrossRef]
23. Mazumder, K.; Hossain, E.; Aktar, A.; Mohiuddin, M.; Sarkar, K.K.; Biswas, B.; Aziz, A.; Abid, A.; Fukase, K. In Silico Analysis and Experimental Evaluation of Ester Prodrugs of Ketoprofen for Oral Delivery: With a View to Reduce Toxicity. *Processes* **2021**, *9*, 2221. [CrossRef]
24. Akram, M.; Egbuna, C.; Uche, Z.; Chikwendu, C.J.; Zafar, S.; Rudrapal, M.; Munir, N.; Mohiuddin, G.; Hannan, R.; Ahmad, K.S.; et al. Chapter 2—Trends in modern drug discovery and development: A glance in the present millennium. In *Drug Discovery Update, Phytochemistry, Computational Tools and Databases in Drug Discovery*; Egbuna, C., Rudrapal, M., Tijjani, H., Eds.; Elsevier: Amsterdam, The Netherlands, 2023; pp. 27–38. ISBN 9780323905930. [CrossRef]
25. Milusheva, M.; Gledacheva, V.; Stefanova, I.; Feizi-Dehnayebi, M.; Mihaylova, R.; Nedialkov, P.; Cherneva, E.; Tumbarski, Y.; Tsoneva, S.; Todorova, M.; et al. Synthesis, Molecular Docking, and Biological Evaluation of Novel Anthranilic Acid Hybrid and Its Diamides as Antispasmodics. *Int. J. Mol. Sci.* **2023**, *24*, 13855. [CrossRef] [PubMed]
26. Anzali, S.; Barnickel, G.; Cezanne, B.; Krug, M.; Filimonov, D.; Poroikov, V. Discriminating between Drugs and Nondrugs by Prediction of Activity Spectra for Substances (PASS). *J. Med. Chem.* **2001**, *44*, 2432–2437. [CrossRef]

27. Mathew, B.; Suresh, J.; Anbazhagan, S. Synthesis and PASS-Assisted in Silico Approach of Some Novel 2-Substituted Benzimidazole Bearing a Pyrimidine-2, 4, 6(Trione) System as Mucomembranous Protector. *J. Pharm. Bioallied. Sci.* **2013**, *5*, 39–43. [CrossRef] [PubMed]
28. Tian, S.; Wang, J.; Li, Y.; Li, D.; Xu, L.; Hou, T. The application of in silico drug-likeness predictions in pharmaceutical research. *Adv. Drug Deliv. Rev.* **2015**, *86*, 2–10. [CrossRef] [PubMed]
29. Tao, L.; Zhang, P.; Qin, C.; Chen, S.Y.; Zhang, C.; Chen, Z.; Zhu, F.; Yang, S.Y.; Wei, Y.Q.; Chen, Y.Z. Recent progresses in the exploration of machine learning methods as in-silico ADME prediction tools. *Adv. Drug Deliv. Rev.* **2015**, *86*, 83–100. [CrossRef]
30. Jia, C.Y.; Li, J.Y.; Hao, G.F.; Yang, G.F. A drug-likeness toolbox facilitates ADMET study in drug discovery. *Drug Discov. Today* **2020**, *25*, 248–258. [CrossRef]
31. Hou, T. Editorial. In silico ADMET predictions in pharmaceutical research. *Adv. Drug Deliv. Rev.* **2015**, *86*, 1. [CrossRef]
32. Zafirah Ismail, N.; Annamalai, N.; Mohamad Zain, N.N.; Arsad, H. Molecular Docking of Selected Compounds from Clinacanthus Nutans with Bcl-2, P53, Caspase-3 and Caspase-8 Proteins in the Apoptosis Pathway. *J. Biol. Sci. Opin.* **2020**, *8*, 4–11. [CrossRef]
33. Banerjee, P.; Eckert, A.O.; Schrey, A.K.; Preissner, R. ProTox-II: A Webserver for the Prediction of Toxicity of Chemicals. *Nucleic Acids Res.* **2018**, *46*, W257–W263. [CrossRef]
34. Velmurugan, D.; Pachaiappan, R.; Ramakrishnan, C. Recent Trends in Drug Design and Discovery. *Curr. Top. Med. Chem.* **2020**, *20*, 1761–1770. [CrossRef] [PubMed]
35. Eder, J.; Herrling, P.L. Trends in Modern Drug Discovery. In *Handbook of Experimental Pharmacology*; Michel, M.C., Barrett, J.E., Centurión, D., Flockerzi, V., Geppetti, P., Hofmann, F.B., Meier, K.E., Page, C.P., Wang, K.W., Eds.; Springer: Cham, Switzerland, 2015; Volume 232, pp. 3–22. [CrossRef]
36. Mayr, L.M.; Bojanic, D. Novel trends in high-throughput screening. *Curr. Opin. Pharmacol.* **2009**, *9*, 580–588. [CrossRef] [PubMed]