The Application of Artificial Intelligence and Drug Repositioning for the Identification of Fibroblast Growth Factor Receptor Inhibitors: A Review

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Abstract

Artificial intelligence talks about modeling intelligent behavior through a computer with the least human involvement. Drug repositioning techniques based on artificial intelligence accelerate the research process and decrease the cost of experimental studies. Dysregulation of fibroblast growth factor (FGF) receptors as the tyrosine kinase family of receptors plays a vital role in a wide range of malignancies. Because of their functional significance, they were considered promising drug targets for the therapy of various cancers. This review has summarized small molecules capable of inhibiting FGF receptors that progressed using artificial intelligence and repositioning drugs examined in clinical trials associated with cancer therapy. This review is based on a literature search in PubMed, Web of Science, Scopus EMBASE, and Google Scholar databases to gather the necessary information in each chapter by employing keywords like artificial intelligence, computational drug design, drug repositioning, and FGF receptor inhibitors. To achieve this goal, a spacious literature review of human studies in these fields—published over the last 20 decades—was performed. According to published reports, nonselective FGF receptor inhibitors can be used for cancer management, and multitarget kinase inhibitors are the first drug class approved due to more advanced clinical studies. For example, AZD4547 and BGJ398 are gradually entering the consumption cycle and are good options as combined treatments. Artificial intelligence and drug repositioning methods can help preselect suitable drug targets more successfully for future inhibition of carcinogenicity.

Keywords: Artificial intelligence, drug repositioning, fibroblast growth factor, receptors

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Introduction

Features of fibroblast growth factors and fibroblast growth factors receptors

Fibroblast growth factors (FGFs) are a family of secreted signaling polypeptides (with molecular mass from 17 to 34 kDa), and their function is regulated by tyrosine kinase receptors and non-signaling proteins causing an intracellular cascade that mediates their biological activity.[1,2] FGFs exist in different organisms, from nematodes to humans.[3]

Purification of these proteins is performed over the last thirty years; according to research, various biochemical and biological functions such as embryo development, organogenesis, tissue ripening, homeostasis, reaction to lesions, neuronal signal transduction, and pathological processes such as angiogenesis, tumor growth, inflammation, and drug resistance have been considered for them. These processes are vital to nearly every aspect of life.[1-3] Several metabolic pathways, such as cholesterol/bile acid balance, maintenance of vitamin D/ phosphate, and metabolisms regulation of glucose/lipid, were conducted by FGF signaling.[4] Therefore, the different functions of FGFs make them a mediator involved in some diseases such as cancer, hypophosphatemia, familial tumor-like

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calcification, congenital craniosynostosis, Kallmann syndrome, dwarf syndrome, cardiovascular disease, chronic kidney disease (CKD), obesity, insulin resistance, type 2 diabetes, and hearing loss, that their signaling is significant in the treatment of these diseases.[5]

Twenty-two structurally related members identified for FGFs had sequential similarity, biochemical function similarity, and evolutionary relations similarity divided into seven subfamilies including FGF1/2/5, FGF3/4/6, FGF7/10/22, FGF8/17/18, and FGF9/16/20.[1]

Studies show that members of the FGFs family are 30–70% similar in their elementary amino acid sequences. A similar central core is present in most FGFs in the inner region with 28 highly conserved and six similar amino acid residues.[3] In the process of binding FGFs to their receptors, ten of these conserved amino acids are involved.[6] There is a β trefoil structure with four-stranded β sheets in the form of a triangular array in the structure of FGF1 and FGF2.[7] Four categories of homologous human receptors have been reported for FGFs: FGFR1 (acidic FGF), FGFR2 (basic FGF), FGFR3, and FGFR which have a sequence similarity of 56 to 71%.[8] All of these receptors show the specific components in their structure[9,10] [Figure 1].[7,11,12]

FGFRs/FGFs signaling pathway

FGFs act in coordination with heparan sulfate proteoglycans (HSPGs)—located at the mast cell surface and within the extracellular matrix—as high-affinity agonists for FGF receptors (FGFRs). The following pathway can be defined for FGF signaling when linked to its receptor [Figure 2].

Following the binding of FGF/HSPG to FGFR, dimerization of monomer receptors occurs in the cell membrane; tyrosine residues located in the cytoplasmic kinase domain undergo autophosphorylation. Subsequently, tyrosine phosphorylation causes the binding of the Src homology (SH2) domain of phospholipase C gamma (PLC-γ) to the receptor and eventually activates the protein kinase C (PKC). PKC activation promotes the signaling pathway of RAS–MAPK and PI3K–AKT through FRS2 and GRB2 adaptor proteins. Jun N-terminal kinase and JAK/STAT pathways are also persuaded by FGFR signaling.[1,10]

Dysregulation of FGFRs/FGFs signaling pathway

The abnormal signaling of FGFRs relates to carcinogenicity in three chief positions: 1) resistance to anticancer agents, 2)

angiogenesis, and 3) mutations in FGFR genes which stimulate the proliferation and differentiation of cancer cells.[2,3,13] Advances in molecular diagnosis techniques and personalized medicine allow the identification of gene mutations involved in many malignancies.[14-18]

Various studies have identified the FGFR signaling pathway as the most frequent signaling route for tyrosine kinase mutants.[19,20] Induction of FGFR mutations may cause erroneous signaling by increased domain kinase activation, modified affinity for FGF ligands, and independent dimerization of receptor ligands.[21-26]

Based on the clinical trials, the advantages of FGFR inhibitors have been demonstrated in breast cancer, brain tumors, gastric, and lung cancer.[27-29]

So, it can be said that understanding the pathogenic mechanisms in FGFs and FGFRs due to mutations, gene mergers, and gene amplifications has resulted in therapeutic approaches for diseases such as chondrodysplasia and craniosynostosis syndromes.[2]

FGFs and angiogenesis

Angiogenesis, as a multi-step process, involves the formation of new blood vessels from pre-existing vessels and plays an essential role in wound, inflammation, embryonic development, and tumor growth.[30] Vessels grow in an unregulated way, under pathological conditions like diabetic retinopathy, cancer of rheumatoid arthritis, and tumor progression.[31] The FGFs family (introduced as the first angiogenic molecule)[32] is one of the angiogenesis inducers.[30] In endothelial cells, expression of FGFR1,2 in vitro has been reported, while expression of types 3 and 4 has not been reported.[33-38] Given the role and importance of FGFs in the vascularization of human tumors, the development of anti-angiogenic therapies with a focus on FGF2, FGF3, and FGF4—particularly FGF2—is a practical and new approach for patient treatment.[9,27,30,39]

In addition to FGFR-targeted therapies, another therapeutic strategy for targeting the extracellular domains of FGFRs has been developed, which creates more opportunities for different isoforms' selective inhibition of these receptors.[40-43]

FGFs and tumor growth/targeting FGFRs signaling in cancer

Tumors are made up of a variety of cancer and stromal cells, including inflammatory cells (macrophage, lymphocyte, and mast cells), fibroblasts, and vascular areas. Stromal
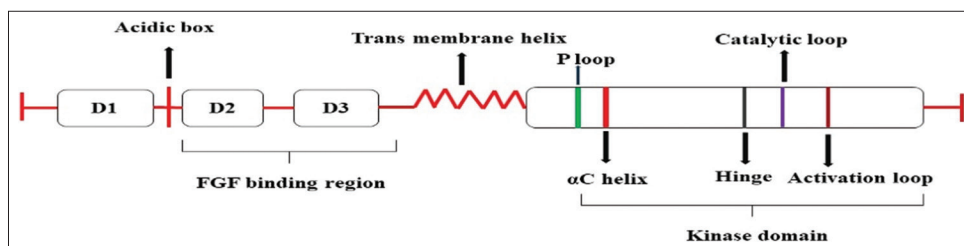

Figure 1: Schematic diagram of fibroblast growth factor receptors. D = Domain
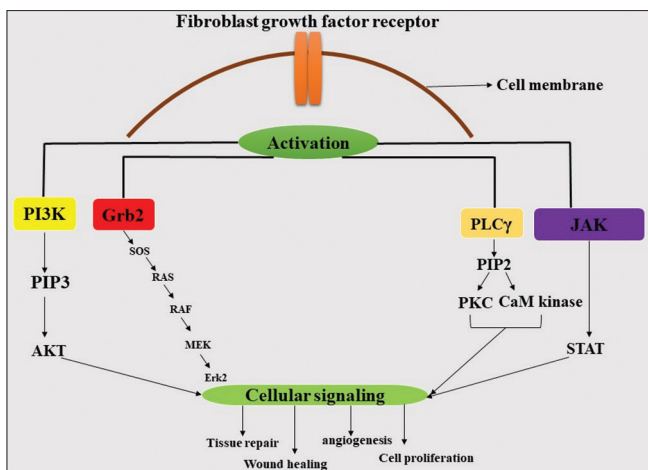
Figure 2: Key signaling pathways of activated fibroblast growth factor receptors. PI3K: Phosphoinositide 3-kinases. PIP2 and 3: Phosphatidylinositol 4,5-bisphosphate and Phosphatidylinositol (3,4,5)- trisphosphate. AKT: Protein kinase B (PKB), also known as Akt. Grb2: Growth Factor Receptor Bound Protein 2. SOS: Son of Sevenless. RAS: Ras GTPase. RAF: Rapidly Accelerated Fibrosarcoma. MEK: Mitogen-activated protein kinase kinase (also known as MAP2K, MEK, MAPKK). Erk2: MAPK1. PLCγ: Phospholipase C Gamma. PKC: Protein kinase C. CaM kinase: Ca2+/calmodulin-dependent protein kinase. JAK: Janus kinases. STAT: Signal transducer and activator of transcription

and parenchymal cancer cells can express different types of FGFRs and release different kinds of FGFs in the tumor environment, creating an intricate system of autocrine and paracrine secretions.

The interaction between the tumor and the host regulates the remaining stages of tumor progression, including cancer cell survival, proliferation, angiogenesis, invasion, metastasis, and response to treatment. Studies have reported that activating FGF/FGFR system plays a significant role in tumor proliferation, differentiation, and resistance to chemotherapy by affecting both tumor and stromal cells.[1,2,10] FGF signaling can be considered a target for cancer treatment. Various types of cancers such as endometrial cancer, ovarian cancer, cervical cancer, hepatocellular cancer, colorectal cancer, small cell lung cancer, gastric cancer, squamous head and neck cancer, breast cancer, prostate cancer, glioblastoma, and melanoma are related to phenomena such as mutation, amplification, overexpression, and translocation of FGFRs.[44,45] This process justifies the necessity of developing FGFR inhibitors.[21,46,47]

Resistance to anticancer therapy

One of the main challenges we face in creating an effective and stable dose for cancer treatment is resistance to treatment.

Interference between the FGFR signaling and other carcinogenic pathways may be involved in resistance to anticancer substances.[48-50] For further understanding of biological response along with resistance to chemotherapy about FGF/FGFR inhibitors, concurrent utilization of next-generation sequencing (NGS) with the ctDNA can help us.[51]

Artificial Intelligence

Artificial intelligence (AI) refers to the modeling of intelligent behavior through a computer with the least human involvement.

The invention of robots led to the world of AI; it is the technology that can think. Of course, this ability to think is very different from what we know as human thinking, but it tries to imitate it. The basis of AI is to define human intelligence and its way of working in such a way that a machine can easily implement it and correctly perform the tasks assigned to it. The purpose of AI is based on three foundations: learning, reasoning, and understanding.

AI is a broad branch of computing concerned with the construction of intelligent machines able to perform tasks that are normally in need of human intelligence. AI is an interdisciplinary science with many approaches but advances in machine learning and deep learning are creating a paradigm shift in almost every part of the technology industry.[52-55]

AI in health

The most considerable point in this field is to improve patient outcomes while reducing costs. Companies active in the health field want to use machine learning to make a better and faster diagnosis and treatment process. One of the most well-known technologies in this field is the IBM Watson system.

Challenges of AI

The application of AI faces many challenges. The main challenge that businesses have to deal with in applying AI is related to people, the requirement of data and information, or business preferences and balances.[56,57]

Drug discovery

Drug discovery is the process of identifying new medications or substances that can be used to treat diseases or conditions. It involves target identification/selection, target validation, lead compound identification, hit-to-lead optimization, preclinical development, clinical development, Food and Drug Administration (FDA) approval, and post-marketing surveillance. The overall goal of drug discovery is to find safe and effective drugs that can be applied to improve human health and treat various ailments. This approach is complex and time-consuming; it is a big challenge to identify an effective drug for a specific disease. At present, AI is widely used in biological and chemical sciences for drug discovery and designing processes.[58-64]

Drug repurposing

Drug repurposing or drug repositioning is the identification of novel therapeutic properties for already existing US FDA-approved drugs. Specifically, a known molecule in usual use or a drug under development for treating specific diseases along with showing a potential effect for a different pathological condition is reinvestigated for that target.[65,66] The progress of a new drug which is an expensive process may take 10 to 15 years. For this reason, since 1995, the number of drugs approved by the FDA has decreased. So, repurposing drugs has appeared as another way of drug development.[67,68] This method

is an AI approach, and its main purpose is to increase the speed and reduce the cost and risk of the drug discovery process.[65]

The two main advantages of this approach are knowing the pharmacokinetics and toxicity of drugs and the low cost of its implementation. In addition, this method is particularly significant in low- to middle-income countries because typical treatments are not economically available to the public.[69-71]

Drug repositioning steps

Both experimental and computational methods can be performed for drug repositioning. An important step in drug repurposing is an in-depth understanding of the genomics and molecular pathways involved in human disease and the activity of drugs to discover new mechanisms, dosage rates, and the achievement of innovative goals. Various approaches available for this method are (1) target-based, (2) drug-based, and (3) disease-based. Target-based approach is associated with the integration of pathway knowledge, disease-associated proteins, and biomarkers to detect a new specific "druggable" goal or mechanism and therapy. Drug-based is based on the resemblance between molecular structures of available drugs, and disease-based is connected with the finding of new planning for drug intermediation in a disease. An example of the identification of a "druggable" disease phenotype includes cidofovir—an antiviral-endowed drug with an antitumor effect for the treatment of papillomavirus-associated tumors. Cidofovir works via the inhibition of FGF-2-dependent metastatic potential of FGF2-T-MAE and melanoma B16 tumors inseminated into mice and zebrafish embryos.[66]

Computational methods aggregate genomic, phenotypic, chemical, pharmacological, and clinical data from various databases, including Gene Expression Omnibus (GEO), Biotechnology Information (NCBI), Drug Bank, PubChem, and PharmGKB. Technologies and bioinformatics approaches such as machine learning, text-mining research, and biological network analysis are useful to obtain thorough data about drugs and diseases. Recent advances in genomics knowledge, disease-related pathways, and the availability of databases support the potential of drug repositioning in personalized medicine.[66] Personalized medicine, also known as precision medicine, is a medical approach that aims to tailor medical treatments and interventions to individual patients. It involves the use of genetic, environmental, and lifestyle information to determine the most effective and safe treatment options for each patient.

Personalized medicine is based on the idea that every individual is unique, and their response to diseases, medications, and therapies can vary. Through personalized medicine, healthcare providers can better understand and predict an individual's susceptibility to specific diseases, select the most appropriate treatment strategies, and adjust drug dosages or interventions based on each patient's specific needs. It holds the potential to enhance patient care, prevent adverse drug reactions, improve treatment outcomes, and optimize resource allocation in healthcare systems. However, it is important to note that the implementation of personalized medicine in routine clinical practice is still an evolving field with ongoing research and technological developments.

So far, many studies have been conducted in the field of AI, drug repositioning, and FGF receptor inhibitors. However, the necessity of a study that can summarize the results of most of these studies and present them in one place is evident. For this reason, we decided to look at the published studies related to these fields in the last 20 years and present their results in the format of a review.

MATERIALS AND METHODS

We performed a broad literature search in PubMed, Web of Science, Scopus, EMBASE, and Google Scholar databases to obtain all available human studies in the past 20 years in related fields. The articles reviewed for this study are available in the mentioned databases.

Search Strategy

Specific human studies published in English that were available between 1997 and 2023—contained in PubMed, Web of Science, Scopus, EMBASE, and Google Scholar databases—were reviewed. Four keyword groups including artificial intelligence, computational drug design, drug repositioning, and FGF receptor inhibitors were used in this study. The search strategy of the PubMed database was used as a pattern to search the other databases.

("Artificial Intelligence" [Mesh] OR Artificial Intelligence [tiab]) AND ("Drug Repositioning" [Mesh] OR Drug Repositioning [tiab] OR drug repurposing [tiab] OR reprogramming [tiab]) AND ("Fibroblast Growth Factors" [Mesh] OR "Fibroblast Growth Factors" [All fields] OR "Receptors, Fibroblast Growth Factor" [Mesh] OR Fibroblast Growth Factor Receptor [tiab] OR FGFR Protein [tiab]) AND ("Meta-Analysis" [Publication Type] OR "Meta-Analysis" OR "Systematic Review" [Publication Type] OR "Systematic Review"). The literature review was conducted on July 2, 2023.

Duplicate studies were removed using comprehensive management software (EndNote 20, Thomson Reuters, New York, NY, USA). After that, in the first stage, the researchers checked the articles' titles and abstracts based on the inclusion criteria. In the second stage, they examined the articles' study designs and the main texts. In the third step, the information extracted from the selected studies was analyzed.

After obtaining relevant studies through searching in the main databases, other sources including gray literature were searched to minimize the number of missing studies.

Selection criteria

Human and animal studies in the fields of AI, computational drug design, and drug repurposing or drug repositioning were used to conduct this review. Original and review studies were taken into consideration as well. Conference reports, articles for which the full text was not available, and also study protocols were excluded.

RESULTS

The article searches and features of the included studies

Using the search strategy, a total of 238 studies were recognized. 139 duplicate and non-related studies through reference management software were detected and removed. Based on the title and abstract assessment, 48 articles met the inclusion criteria. Finally, 26 articles were selected for the terminal analysis based on full-text retrieval [Figure 3].

Application of drug repositioning for the design of FGFRs inhibitors

Because cancer is one of the deadliest diseases known, many efforts are made to find more effective and safer alternatives using drug repurposing. For example, many studies have been conducted on cardiovascular drugs for antitumor therapy.[72]

Considering that FGF receptors, which are among receptor tyrosine kinases, are dysregulated in cancers, they have become key drug targets in the last two decades. To date, 62 kinase inhibitors have been approved, of which fifty-two kinase inhibitors are TKI. Failed TKIs are used by the drug repositioning approach to discover new applications.[68,73-75]

Classification of anti-FGFR drugs with IC50 < 100 nmol against at least one FGFR based on drug repositioning

Overall, there are two different classifications of FGFR inhibitors. The first class is "multitarget" TKIs or nonselective FGFR TKIs which often target VEGFRs and generally have

remarkable bioactivity against the FGFR family. Highly bioactive FGFR or selective FGFR TKIs are the second class. Selective inhibitors were developed to dominate the off-target effects of nonselective inhibitors. Here, we mention some of them that have entered the clinical phases and are being used:[76]

TKI258 (dovitinib), BIBF1120 (nintedanib), E3810, E7080 (lenvatinib), BMS582664 (brivanib), ENMD-2076, TSU68 (orantinib), AP24534 (ponatinib) are multitargeted TKIs. AZD4547, BGJ398, LY2874455, monoclonal antibodies such as MGFR1877S, and finally FGF traps such as HGS1036/FP-1039 are selective TKIs.[77-88]

Selective Anti-FGFR TKIs

1. AZD4547 (a highly active FGFR selective inhibitor), BGJ398, and LY2874455 as selective FGFR TKIs have been evaluated for clinical phases.
   AZD4547 is a selective kinase inhibitor that suppresses FGFR1-3 signaling and growth in tumor cell lines. In phase II clinical trials, AZD4547 is estimated. For example, in the study of Gavine PR and Chell V et al., oral administration of AZD4547 in a representative FGFR3-driven human tumor xenograft model induced antitumor activity.[85,89]
2. BGJ398 is the next selective inhibitor of FGFR1-3.[86] Successful results of using this type of inhibitor to reduce tumor-induced lesions in amplified lung cancer have been reported in some studies.[90]
3. LY2874455 is examined in phase I clinical trial and is more potent *in vivo* evaluation in FGFR1-4 inhibiting than VEGFR[87] [Table 1].

Nonselective FGFR TKIs

1. Dovitinib (TKI258) has antitumor and antiangiogenic activities by inhibition of VEGFR, PDGFR, and FGFR.[77] One of the trials conducted with this drug has reported that its use in 35 patients with advanced solid tumors had positive effects except for side effects such as fatigue and digestive disorders. For instance, one melanoma patient had a partial answer to the treatment, and two patients had a stable condition of the disease for six months or more.[91] The results of a clinical trial study with 45 patients with advanced melanoma, except for side effects such as dehydration and fatigue, diarrhea, abdominal pain, and anorexia are associated with an increase in plasma levels of VEGF and FGF23 at the beginning of the treatment cycle. Also, FGFR1 inhibition has been reported.[92] In addition, in the phase II of a clinical study regarding patients with HER2-negative breast cancer—previously treated, metastatic, and under-treated with dovitinib—the antitumor activity of it was seen to inhibit amplified/HR-positive subset-FGFR1.[93] Today, this drug is being evaluated in phase III of the clinical trial as the third line of treatment for patients who have already been treated with mTOR inhibitors and VEGFR-TKI.[94]
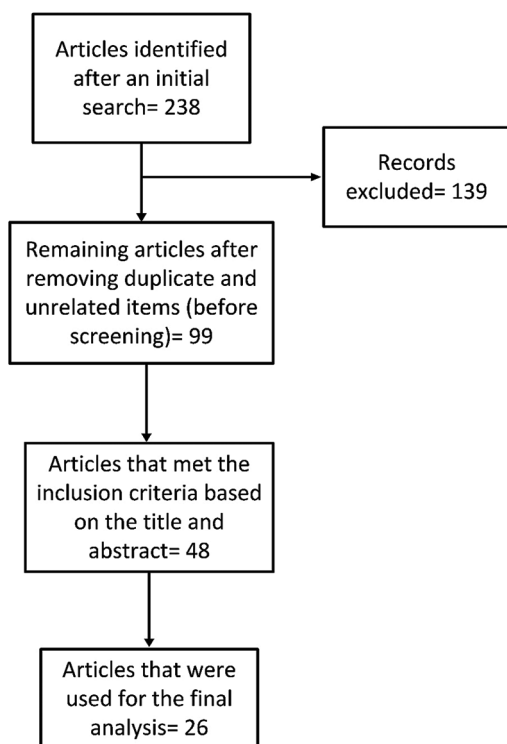2. E3810 is a strong inhibitor of CSF-1R, FGFR1,2, and VEGFR1–3.[79] E3810 was tested in a phase I clinical


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Articles identified
after an initial
search= 238
        │
        ├──────────────→  Records
        │                  excluded= 139
        ↓
Remaining articles after
removing duplicate and
unrelated items (before
screening)= 99
        ↓
Articles that met the
inclusion criteria based
on the title and
abstract= 48
        ↓
Articles that were
used for the final
analysis= 26
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Figure 3: Articles identified in the stages of screening, qualifying, and entering the review

Table 1: Fibroblast growth factor receptor inhibitors identified using drug repositioning

Inhibitor name	Original indication	Target	CT phase	Reference
AZD4547	Antitumor activity	FGFR1-3 signaling	II, The drug is gradually entering the consumer market	[85, 89]
BGJ398	Reduction of tumor-induced lesions in amplified lung cancer	FGFR1-3 signaling	II, The drug is gradually entering the consumer market	[86, 90]
LY2874455	Multiple myeloma cancer	FGFR1-4 signaling VEGFR2 signaling	I	[87]
Dovitinib/ TKI258	Advanced solid tumors, Melanoma patient, Breast cancer	VEGFR signaling PDGFR signaling FGFR1 signaling	III	[91]
E3810	Advanced solid tumors	CSF-1R signaling FGFR1,2 signaling VEGFR1–3 signaling	I	[79]
Nintedanib/ BIBF1120	Idiopathic pulmonary fibrosis, Systemic sclerosis-associated interstitial lung disease	FGFR signaling PDGFR signaling VEGFR signaling	I	[78]
Ponatinib/ AP24534	Chronic myelogenous leukemia, Acute lymphoblastic leukemia	FGFR signaling	II	[96]
Brivanib/ BMS582664	Antitumor activity, Hepatocellular carcinoma	VEGFR signaling FGFR signaling	III	[80, 82, 83, 97, 98]
Orantinib/ TSU-68	Antitumor activity, Lung Cancer, Breast Cancer, Kidney Cancer, Gastric Cancer, and Prostate Cancer	VEGFR signaling FGFR1 signaling	III	[80, 82, 83, 97, 98]
ENMD-2076	Antitumor activity, Hematopoietic cancer, Multiple myeloma, Advanced Cancer	VEGFR signaling FGFR signaling	I	[80, 82, 83, 97, 98]
lenvatinib/ E7080	Antitumor activity, Thyroid cancer, Renal cell carcinoma, Hepatocellular carcinoma	VEGFR1, 2, 3 signaling FGFR1-4 signaling PDGFRα signaling	Approved by FDA*	[80, 82, 83, 97, 98]

*Food and Drug Administration

trial in advanced solid tumors. Side effects such as hypothyroidism, proteinuria, and hypertension have been noticed. In some patients, a partial response to treatment and stable disease status were observed.[95]

3. Nintedanib (BIBF1120) is an oral derivative of indolinone that inhibits FGFR, PDGFR, and VEGFR. In the phase I trial in Japanese patients, usage of BIBF1120 led to stable disease status in 76% of patients, but an increase in hepatic enzyme was also reported.[78]

4. Ponatinib (AP24534) is a multikinase inhibitor of BCR–ABL. This drug is under investigation in phase II of clinical trials in chronic myelogenous leukemia and acute lymphoblastic leukemia. AP24534 is an FGFR inhibitor in experimental assays, and *in vitro*, it was able to block cell proliferation. Based on these results, ponatinib is introduced as a possible treatment for solid tumors.[96]

5. Compounds such as brivanib/BMS582664, orantinib/ TSU-68, ENMD-2076, and lenvatinib/E7080 are VEGFR inhibitors, but they also have anti-FGFR activity.[80,82,83,97,98]

Based on the studies, it is determined that nonselective FGFR inhibitors have the potential to be used for cancer management and therapy. However, the chief toxicity stays for inhibition of VEGFR.[99] In general, based on the published articles, it can be said that multitarget kinase inhibitors are the first drug class to be approved, due to more advanced clinical studies. Inhibitors such as AZD4547 and BGJ398 are gradually entering the market and consumption cycle and are good options as combined treatments.[95] In the drug design field, we had considerable advances in the second-generation selective FGFRs inhibitors, although the complex nature of FGF/FGFR signaling needs expanded research; multiple factors affect the response to therapy[76] [Table 1].

DISCUSSION AND CONCLUSION

Drug repositioning is a new and effective strategy, wherein existing drugs are assessed for new therapeutic uses beyond their original intended indications. This approach aims to identify new ways to repurpose approved or investigational drugs for different diseases or conditions. Drug repositioning can potentially save time and resources compared to de novo drug discovery (the main objective is to identify and develop entirely new drugs to target specific diseases or conditions). According to the reviewed studies, using AI systems, this approach can introduce new drug targets for the inhibition of different receptors like FGFRs. These strategies will be

helpful for patients that have pharmacological resistance to current medication, mainly in low-income countries—as the required time and cost to produce a new drug will be saved. Besides, the drugs designed with this approach are based on the mechanism, and the treatment with them will be more targeted.

Inhibition of FGFRs using small molecules suggests a new and practical approach for cancer therapy induced by aberrations of FGFRs. A deep comprehension of the tissue-specific nature of the FGFRs signaling pathway and its integration with the AI and drug repositioning methods can help in the more successful treatment of tumorigenesis and different types of cancers. According to published reports, nonselective FGFRs inhibitors can be used for cancer management, and multitarget kinase inhibitors are the first drug class approved due to more advanced clinical studies. For example, AZD4547 and BGJ398 are gradually entering the consumption cycle and are good options as combined treatments. So, drug repositioning use can successfully design and run models to preselect suitable drug targets for inhibition of tumor development and carcinogenicity in the future.

Future perspective

AI and drug repositioning hold immense potential for identifying new drugs and therapeutic uses. Drug repositioning and AI can increase efficiency, repurpose existing drugs, treat rare diseases, and malignancies such as cancer, reduce costs, accelerate drug discovery, enable personalized medicine, and facilitate combination therapies; they are expected to revolutionize drug discovery and reshape the pharmaceutical industry in the future.

The design and implementation of such studies by providing new insights related to personalized medicine can be a basis for preliminary planning and providing correct interventions to improve the quality of life of patients; their results can strengthen the relationship between research and the clinic.[100]

Limitations

Lack of comprehensive data and literature, limitation of complete knowledge about the underlying molecular mechanisms, and the difficulty in the interpretation of complex data about AI and drug repositioning are the most significant limitations of this study.

Acknowledgment

Conflicts of interest

There are no conflicts of interest.

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