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Design, Synthesis Strategies, Future Prospects, and Anticancer Activities of Different Derivatives as Novel Agents

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Abstract | **Review Article**

The design and synthesis of pyrimidoquinoline derivatives were systematically explored to address the urgent need for novel, potent anticancer agents with improved selectivity and reduced systemic toxicity. This research focused on the strategic integration of the pyrimidine and quinoline scaffolds, two pharmacologically significant heterocycles, to farm a fused tricyclic system capable of multi-target inhibition. Various synthetic methodologies, including multi-component reactions and microwave assisted cyclization, were employed to generate a diverse library of derivatives. These strategies were guided by Structure Activity Relationship (SAR) analyses, which highlighted the critical role of specific functional group substitutions particularly at the C-2 and C-4 positions in Modulating Electronic Properties (MEP) and Enhancing Molecular Minding (EMM) affinities within the ATP-binding pockets of protein kinases. The anticancer potential of the synthesized compounds was rigorously evaluated through *in vitro* cytotoxic analyses against a collection of samples of cancer cells, including breast (MCF-7), lung (A549), and colon (HCT-116) carcinomas. Several derivatives show significant antiproliferative activity, with IC_{50} values in the sub-micromolar range, outperforming standard reference drugs in specific instances. Mechanistic investigations, including flow cytometry and Molecular Docking Simulations (MDS), indicated that the most active compounds induced apoptosis and effectively inhibited angiogenesis-related signaling pathways. Future prospects for this scaffold were identified in the optimization of pharmacological profiles through the development of nano-formulations and targeted drug delivery systems. The study concluded that the pyrimidoquinoline molecule act as a reliable for the development of next-generation chemotherapeutics. The successful synthesis and biological validation of these derivatives provided a foundational roadmap for future clinical evaluations, positioning them as promising potential compounds in the ongoing effort to overcome multidrug resistance in oncology.

Keywords: antiproliferative, anticancer strategies, cytometry, chemotherapeutics, Pyrimidoquinoline.

1. INTRODUCTION

Cancer is one of the most dangerous and refractory diseases that threatens human health. Novel anticancer pharmaceuticals are latest cancer therapies that do not include surgical intervention, radiotherapy, and annihilator. Among them are hormones, antibodies, and small molecule inhibitors. Conventional chemotherapy has been substituted by novel anticancer drugs as the first line treatment for numerous malignancies, with new and growing indications for these drugs. Small molecule inhibitors subsequent stage indication that could differently allow tumefaction development also increase by acting on intracellular or cell surface targets. Chemotherapy antibodies can serve like biological therapeutic drugs or growth factor receptors [1]. The future study by hindering malignant cells from using coping mechanisms against the immune system. Estrogenic drugs operate by reducing hormonal

concentrations that are vital for some cancer cells to develop. To increase survival and reduce morbidity, cancer treatment regimens frequently incorporate new anticancer drugs and traditional chemotherapy, either alone or in combination. When evaluating response on imaging, the radiologist will benefit from having a basic understanding of anticancer drug classification.

One of the main causes of death in the globe is cancer, as well as its occurrence significant in the modern world. The three most prevalent cancers in 2020 were colon, lung, and breast cancer. Additionally, it is predicted that there will be 28.4 million instances of cancer in 2040, a 47% rise from 2020. As a result, numerous novel, inventive, and targeted medications that target cancer cells are being sought after [2]. These initiatives aim to lower the expense and adverse effects of chemotherapy. The study and development of novel small compounds that target tubulin structure and function is one potential tactic meant to reduce toxicity toward healthy cells during treatment [3].

The incidence of cancer is steadily rising globally, making it a global health concern. Genetic alterations and overexpression of several protein kinases (PKs) are linked to a number of cancer forms. As a result, PKs have recently drawn a lot of interest as biological targets growth of novel focused medicines, management, and cure of the majority of cancer types. Phenmiazine is a special core structure, and numerous its analogs have been shown to have strong chemotherapeutic and PKs inhibitory effects [4]. The FDA has clinically authorized vannetanib (I), a powerful dual VEGFR and EGFR tyrosine kinase inhibitor, to alleviate metastatic thyroid cancer. Furthermore, it has been descried to forbid expansion of breast cancer cells via enhancing cellular death. Fresh quinazoline derivation with vascular endothelial growth factor receptor 2 inhibitory effect is cediranib (II), which is mostly given for advanced bowel, hepatic, and pulmonary carcinoma. Moreover, derazantinib (III), a fused quinazoline derivative, is a strong inhibitor of FGFR1-3 and VEGFR-2 that may have antitumor effects [5].

A polyphenol named resveratrol additionally shown to destroy a number of individual sarcoma cells by means of apoptosis processes similar necroptosis, and autophagy. Trans-(E)-resveratrol has a number of pharmacological and biological effects and is harmless [6]. But resveratrol's potential as an anticancer drug is limited because of its short half-life, unstable double bond, and quick metabolism and excretion. Consequently, a lot of research is being done on resveratrol derivatives and analogues that potentially improve resveratrol's anticancer properties and address its drawbacks [7].

The production of structurally varied molecules has been the subject of substantial research due to the search for up-to-date anticancer medications. The heterocyclic rings 1-oxindene and benzofuran scaffolds are highly favored and extensively researched for emergence of innovative, potentially antineoplastic drugs [8]. High biological activity based on heterocyclic molecules makes them essential in organic and pharmaceutical chemistry. Their pharmacological significance in a variety of contemporary medicinal agents, making them essential building blocks for the development of novel drugs. A broad range of biofunction, such as antiviral, germicida, dideoxycytosine, anesthetic, antioxidant, sulfonylureas, antiepileptic, antihypertensive, aminoglycosides, fluoxetine, and antimycotic properties, are possessed by compounds with a furan and benzofuran ring [9]. Derivatives of tetrole and cumarone demonstrate significant and widespread biological function against a variety of tumors, including mammalian (MDA-MB 231), lung (A549), hepatocellular (HepG2), glandular (DU145), colorectal (HCC-2998), adenoma, tubercle (A375), epithelioma (B16-F10), dysgerminoma (IGROV1), leukemia (MOLT-4), hypernephroma (RXF 393), CNS (SNB-75), polyp (SK-MEL-2), and rectal carcinoma (SW480) [10].

One recently identified alkaloid with a unique spiro structure is penicitrinine. The compound was isolated from the fungus Penicillium citrinum, which is marine in origin. It shown antiproliferative activity against a number of tumor types, including A-375 malignant melanoma, gastric, bronchogenic, colon, epidermoid, hepatic, cantonese, esophageal, breast, and black lung crab. Essential anticancer macromolecules, sulfated polysaccharides have several commercial, biological, and therapeutic applications [11]. It has been thoroughly studied for its anticancer efficacy because of its therapeutic potential against malignant cells, specifically through cell cycle arrest, apoptosis induction, reduction of angiogenesis, and control of inflammatory responses [12].

Neopeltolide is a chemical with intriguing structure and biology activities that can be used as a lead in the synthesis of anticancer medications. Several cancer cell cultures, such as A549 alveolus, murine, MCF-7 breast, HCT-116 colorectal, and kidney carcinoma, exhibit strong antiproliferative effects *in vitro* [13].

In the past two decades, about 25% of pharmaceuticals have been directly obtained from plants. Etoposide chemotheraptic action multitudinous cancer cells may be modulated by polyphenols. When combined with etoposide, the majority of polyphenols increase cell apoptosis, damage DNA, and stop the cell cycle. Previous studies to the development of efficient techniques for collecting and administering polyphenolic medicines, comprehensive in vivo research is necessary to explore feasible use of phenols in etopophos chemotherapy. In 1983, toposar was authorized for Patient treatment in the America, it is still often used in

chemotherapy for lung, gonadal, leukemia, adrenal cortex, breast, and brain tumors, among other disease types [14].

Derivatives of piperazine (Fig-1) have become favored pharmacophores with a number of therapeutic uses. Several approved marketed pharmaceuticals that contain 1,4-diazacyclohexane moieties include normarex (sedatives), remydrial (ophthalmic solutions), and piperaquine (antiparasitic drug). Other approved commercial drugs that contain piperazine include rociletinib (lung cancer drug), olaparib, verzenio, and ibrance (breast cancer drugs), and Imatinib (drastic lymphoblastic leucaemia antidots) [15].

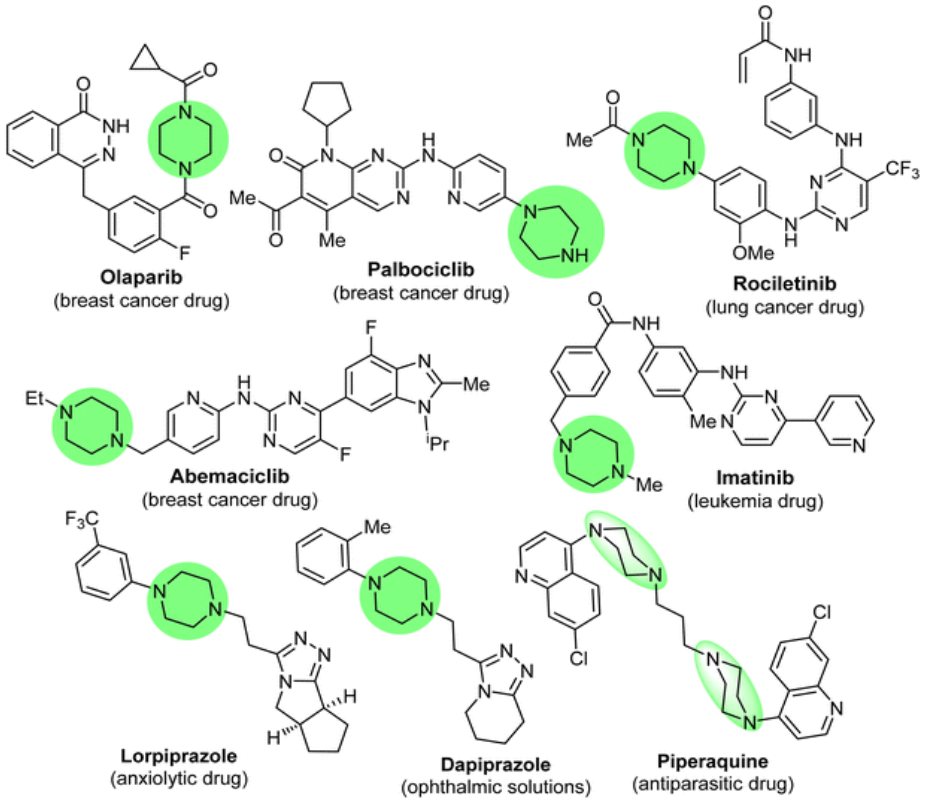

Figure 1: Piperazine brand as new drugs.

The wide range of inhibitory effects of 1,3,4-thiadiazole derivatives, especially 1,3,4-thiadiazoles, which are extremely important as powerful anticancer drugs, render them exceptional pharmacological agents [16]. Certain FDA-approved anticancer medications, including azeteta, litronesib, and filanesib, were also discovered to use the 1,3,4-thiadiazole moiety (Fig-2).

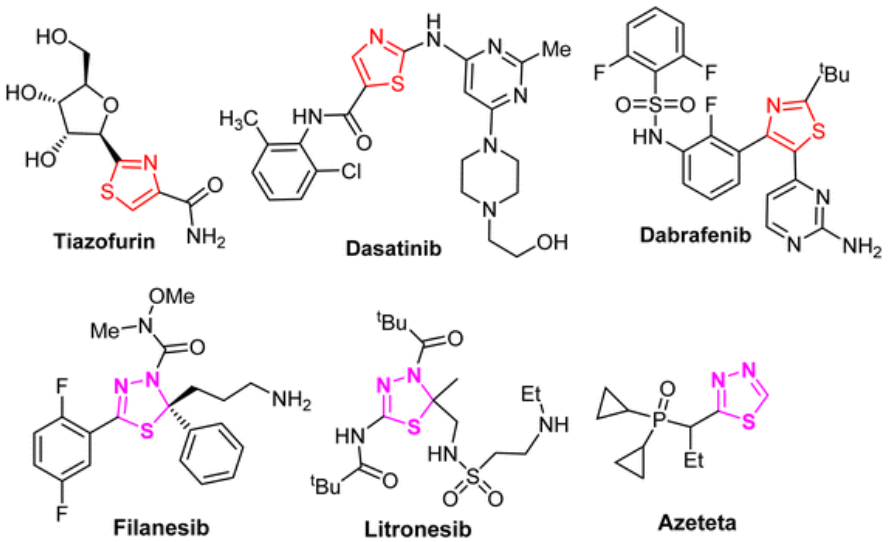

Figure 2: Antitumor incorporating 1,3,4-thiazole motifs

Blend based on synthetic bis-carboxamid (Fig-3) considered a variety of inhibitory actions, including anticancer capabilities. Derivatives of bis-carboxamides were used as key components of di anticancer medications, commercialized medications, lacosamide and batimastat.

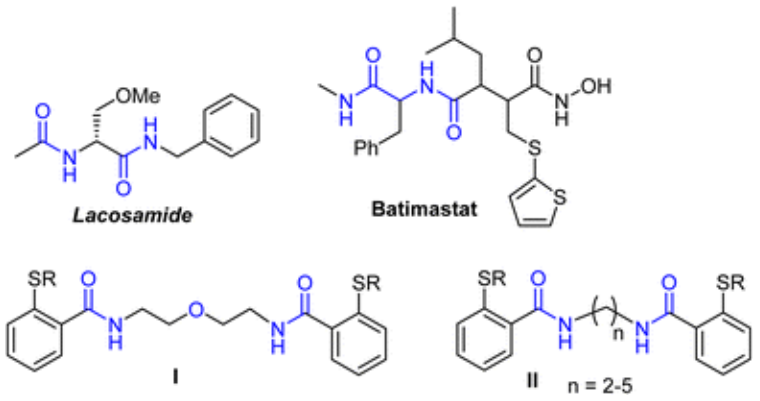

Figure 3: bis-carboxamide as Antineoplastic

Cancer is a deadly illness that can strike anyone, anywhere in the world. According to 2020 GLOBOCAN report, an international association for cancer research, which covers studies on 185 countries worldwide 36 distinct carcinomas, grim numbers show that 10.3 trillion people have departed from cancer, 19.3 million novel cases have been distinguished. Although research on cancer cell biology has advanced significantly since the 1950s, most cancer treatments still include radiation, annihilator, surgical operation, continuing to be majority commonly used pharmaceutical strategy [17]. When applied in real life, these tactics have several disadvantages. Although cancer can affect people of any age, including fetuses, the risk of most types of the disease rises with age. It has been concluded that cancer is an inflammatory illness as a result of research showing obvious correlation between swelling and cancer throughout time. Heteroatoms, particularly heterocyclic blocks, present a significant opportunity to find new cancer treatment molecules [18]. Since then, comprehensive range FDA-approved drug prospects have consistently used the privileged scaffold pyridine (Fig-4). Azine, in its various alternate forms, is valuable source of clinically efficacious medications and occupies a key place in medicinal chemistry research. It is the fundamental building block of more than 7000 medications now on the market. Sorafenib, Crizotnib, Regorafenib, and Vismodegib are the anticancer medications that are currently on the market and have pyridine scaffolds [19]. Several medications, such as Ivosidenib, Lorlatinib, Apalutamide, and Abemaciclib, approved by FDA in recent years for cancer treatment. The development of a number of chemotherapeutic medications has advanced significantly, yet optimum therapeutics that is, extremely effective medications with minimal side effects remain elusive. Research on new bioactive compounds is nevertheless encouraged to proceed [20].

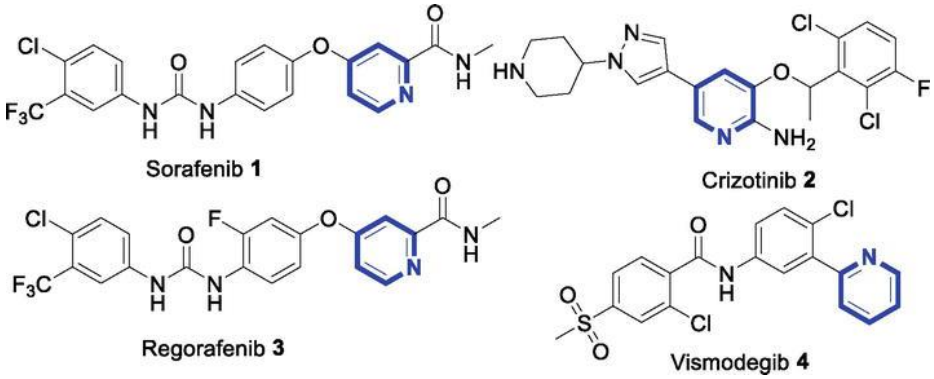

Figure 4: pyridine based componds as anticancer drugs.

2. Strategies for Synthesis of Novel Anticancer Agents

2.1. Marine natural products

There are many biologically active compounds found in the marine environment that is able to treat human ailments, particularly cancer [21]. Several anticancer narcotics derived from saltwater amalgamations have been approved for clinical use, including cytosine, vidarabine, arranon, fludarabine, inorganic phosphate, trabectedin, halaven, brentuximab vedotin, blenrep, plitidepsin, and zepzelca. Glucose from seaweed have been suggested even as pertinent ancillary for cancer care or utilized precisely for manipulation, in addition to phlorotannins [22].

2.2. Pyrimidoquinoline Derivatives

New N-aryl-5-aryl-6,7,8,9-tetrahydropyrimido [4,5-b] quinolin-4-amines have been discovered. By using amidine rearrangement of intermediates 3a–3c, 4a–4l were farmed as possible anticancer agents. When compared to lapatinib, the reference drugs, pyrimido[4,5-b] quinolines demonstrated encouraging action antagonistic towards MCF7 Cells. The cytotoxic activity of compounds was higher relative to lapatinib [23].

2.3. Aurone and Indanone Derivatives

A class of synthetic and natural molecules known as hemiindigoids are considered a backbone of aromatic hydrocarbons and are highly active biological compound. Two compounds, aurone (2-(Z)-benzylidene-3-(2H)-benzofuranone) and analogue indanone 2-benzylidene-3-(cyclohexylamino)-2,3-dihydro-1H-inden-1-one hydrochloride, are hemiindigoid scaffolds (Fig-6). It has been described that aurones (Fig-5) and indanone possess antitumor, antimicrobial, antiinflammatory, hypoglycemic, and antioxidant qualities [24]. The inhibitory effects of 75 compounds were evaluated using MTT analyses descried to quartet malignant cells HT-29, HepG2, A549, and HELA. According to the findings, thirty substances had antitumor efficacy that ranged from moderate to good. Five of these compounds (A_3, E_3, E_8, F_2, and F_4) had address an efficiency against HT-29 cell lines that was equivalent to positive reference [25].

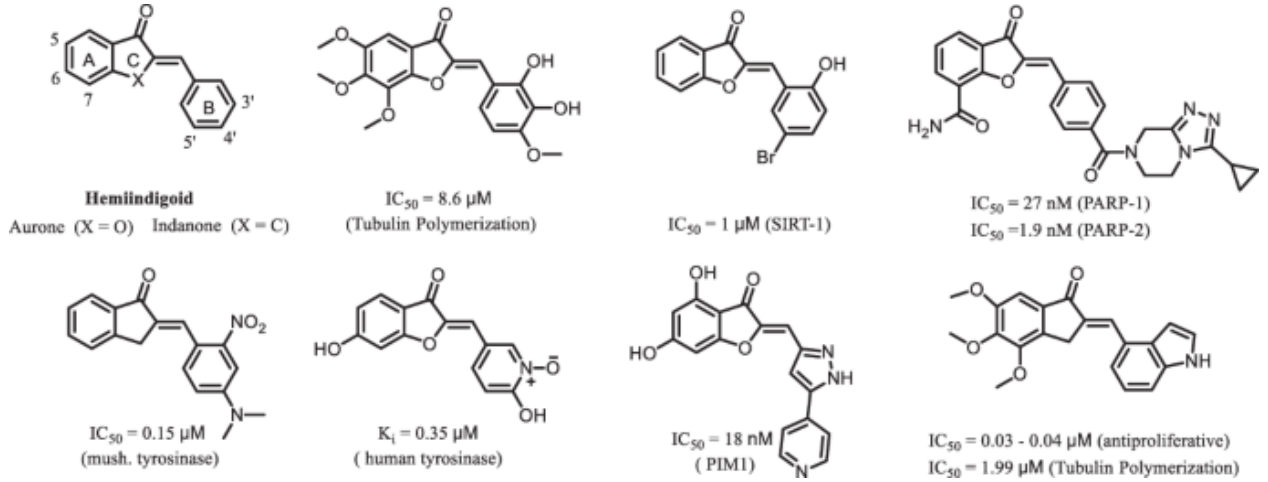

Figure 5: aurones as Anticancer

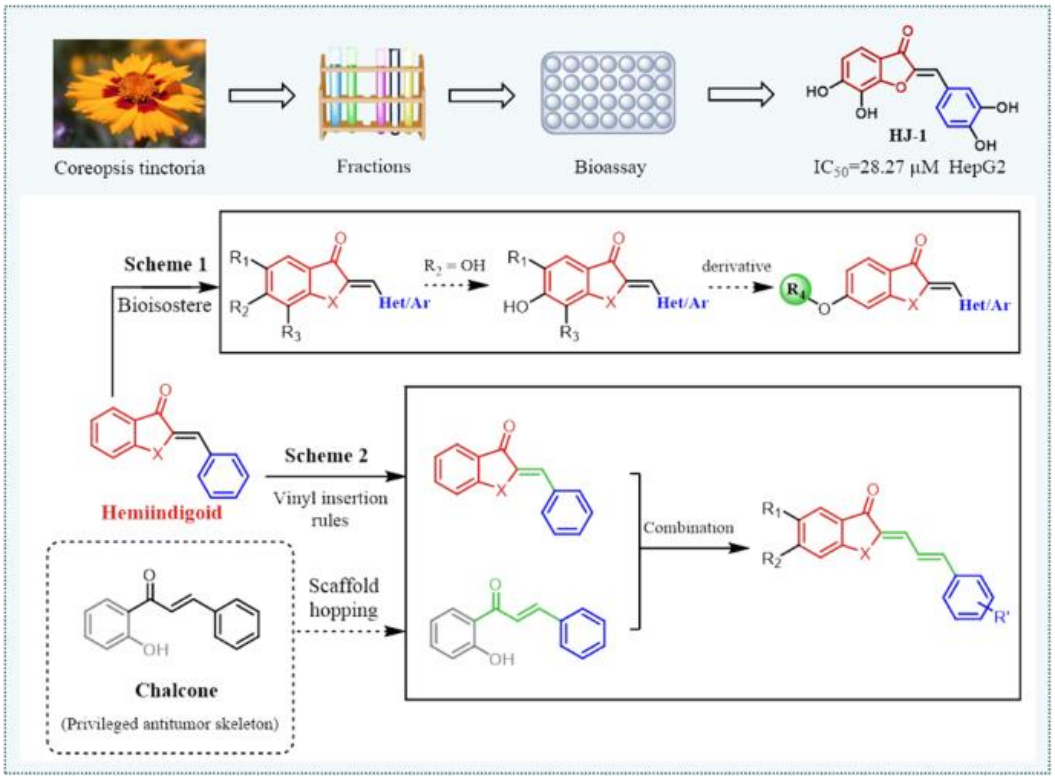

Figure 6: Hemiindigoid skeleton modification strategies.

2.4. Anticancer Peptides (ACPs)

The databases contain a number of ACPs, such as the anticancer database APD3, which can be used for therapeutic intervention against several kinds of cancer [26]. These include A59, Ehlrich's murine ascites cells, and Magainin 2, which forms openings when cytoplasmic membrane disruption occurs to provide anticancer effects against adenocarcinoma. Brevinvin from Limnonectes fujianensis destroys lung cancer H460, glioblastoma U251MG, melanoma cells, and colorectal cancer by penetrating the lipid bilayer [27].

2.5. Recent Green Chemistry

Pyrimidine derivatives are synthesized using environmentally friendly methods that are profitable and thought to be faster and more accurate because they only take a few minutes to produce substantial product. We also evaluated cancer fighting properties of these derivatives' hostile to extensive range of leucaemia cell lines. Zidovudine and Stavudine are anti-HIV, 5-Fluoracil is carcinopreventive [28].

2.6. Coumarin Azole Hybrids and Chalcones

A significant class of nitrogen heterocycles, azoles are found in fragments in a number of anticancer drugs. Promising biological agents that increase pharmacological activity are coumarin azole hybrids. This has led to the selection of these hybrids for the formulation of anticancer drugs [29]. The flavonoid class of natural products includes chalcones composed of two arenes united with an enone. By constituting the central core of the physiologically active coumarin molecule, they exhibit anticancer action. Accordingly, they contribute an important role in drug discovery process [30].

2.7. Nanotechnology

Interestingly, drug carriers are essential to anticancer treatment because they enhance the effectiveness and transport of therapeutic substances while reducing adverse effects. In anticancer therapy, NP, nanocapsules, nanoemulsions, and hydrogels are only a few of the several drug carrier forms that can be used. Furthermore, many signaling pathways can be exploited by these nanotechnology based anticancer medications to stop carcinogenesis [31]. FDA have approved a number of nanomedicines for the treatment of cancer. These therapeutics use the special qualities of nanoparticles (NPs) to improve drug delivery and efficacy. A liposomal version of doxorubicin, Doxil® is used to treat multiple myeloma and ovarian cancer, among other malignancies. Albumin NPs are used in Abraxane®, a chemotherapy medication, to administer paclitaxel. Metastatic pancreatic cancer can be treated with Onivyde®. Acute myeloid leukemia is treated with Vyxeos® (Daunorubicin and Cytarabine Liposome), it is a daunomycin and cytarabine combination based on liposomes. With better targeting and lower toxicity than conventional formulations, these nanomedicines mark important breakthroughs in cancer treatment [32].

2.8. Betulinic acid

Nowadays, mammary carcinoma is the bulk prevalent type of leukemia globally. According to most recent global cancer burden data, 2.3 million new instances of breast cancer are expected to occur worldwide in 2020, making up 11.7% of all cancer cases worldwide. Lupatic acid is a pentacyclic triterpene molecule that might be produced through combination reaction, biotransformation, and separation [33]. Platanol possesses outstanding botanic properties, and potential to treat breast cancer in particular merits consideration. Its primary mechanisms are induction of mitochondrial redox imbalance, monitoring of distinct protein gene regulators, and blockage of glucose metabolism, NF-κB pathway, and breast cancer metastases. Additionally, betulinic acid (Fig-7) can lessen the harmful side effects of chemotherapy medications like paclitaxel and build malignant neoplasm of breast more sensitive towards them [34].

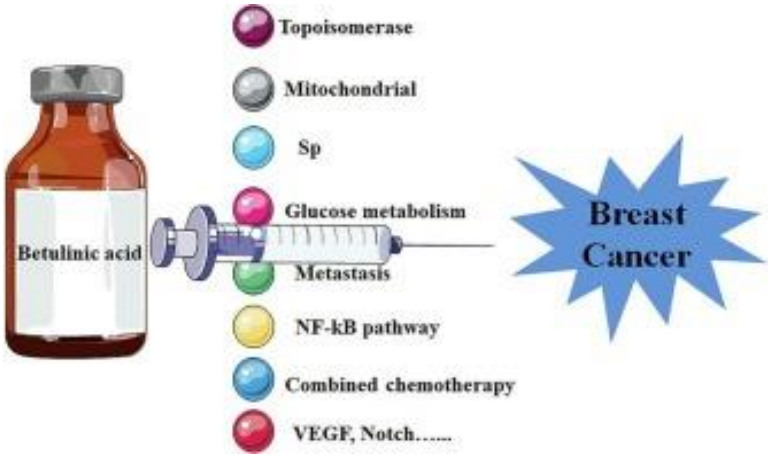

Figure 7: Betulinic acid in Chemoprevention

2.9. Metal Complexes

Metal complexes and their derivatives have special qualities and capacity to stop tumor growth, also used as anticancer drugs. Despite being widely used and acknowledged for their effectiveness in cancer treatment, platinum based medications are frequently linked to

serious toxicity and adverse effects [35]. Thus, researchers have concentrated their efforts on farmed novel metal-based complexes (Fig-8) that might be more effective or less harmful than drugs based on platinum. Because of their capacity to interact with DNA and other macromolecules and cause cell death, certain mineral based mixtures applied in lymphoma therapy [36].

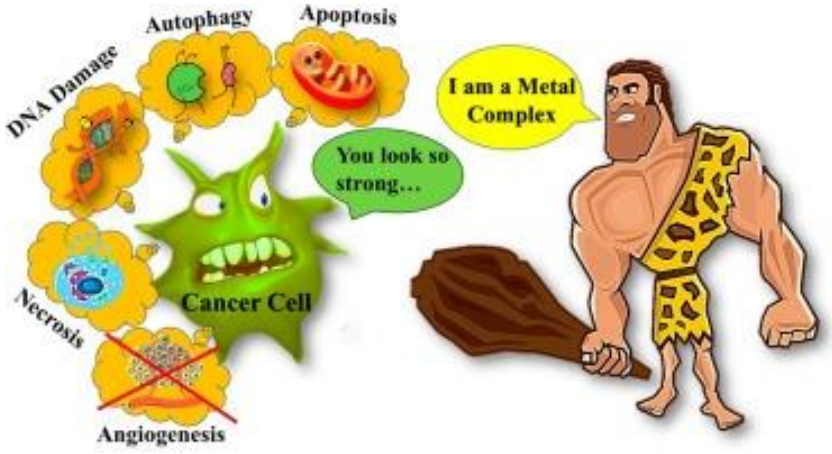

Figure 8: Latest developments in metal-based anticancer agents

3. Limitations

The development of new anticancer drugs has progressed significantly; however, several limitations still hinder to restrict their widespread application and efficacy. A few of those restrictions are:

1. Resveratrol is a naturally occurring polyphenolic stilbene that has been extracted from a variety of foods, plants, and drinks. It modulates a wide range of targets and signaling pathways to display diverse organic and healing effects [37]. Particularly, its capability for implementation, chemoprevention and remedies of different malignancies has garnered considerable attentiveness as for encouraging along manifold anticancerous drug [38]. However, its applications were limited by adverse pharmacokinetics/pharmacodynamics profile, which included poor absorption. To get over these restrictions and boost anticancer effectiveness, numerous new resveratrol derivatives and analogues utilizing various modification techniques should be employed [39].
2. More study is needed to maximize new anticancer agents' selectivity towards cancer cells, limit off-target effects, and lower toxicity. Increasing the accumulation of unique antitumor compounds in tumor tissues while preserving healthy cells requires the design and development of more efficient and selective targeted delivery mechanisms [40].
3. Effective and innovative medications are desperately needed to treat a wide range of illnesses, and it's critical to comprehend the role that metal-based medications play in cancer treatment. It is necessary to review the clinically approved remedies for cancer in order to recognize noteworthiness of metallobased pharmaceuticals in eradicator [41].
4. Anti-neoplastic medications, which are currently used to treat cancer, have a number of harmful reactions, mostly target fast dividing cells rather than only malignant ones. Therefore, an alternate anticancer medication is offered by anticancer peptides (ACPs). Because they distinguish between lump and benign cells, interconnect with electronegative membrane modules differently in cancerous and non-cancerous cells. None of these strategies have reached the market despite the numerous successful in vivo research on ACPs that have been published. Proteins bad absorption, their morbidness, the immune reaction to prescriptions, and overpriced methods are obstacles to employing anticancer peptides ACPs in cancer treatments.
5. There are significant rates of morbidity and mortality linked to hepatocellular carcinoma (HCC). The main therapy approach for HCC is chemical medication; nevertheless, its effectiveness is diminished by minimal feedback and therapeutic opposition. The need for brand new, functional medications is therefore urgent, and numerous researchers have worked to find anti-cancer medications derived from marine species.
6. For many years, platinum-based chemotherapeutics have been essential in the field of oncology. However, the development of serious side effects and medication resistance limits their wider applicability. Current research has accelerated the hunt for alternative agents, especially non-platinum coordination composites. It is difficult to design effective standard metal compounds that target gene.
7. The treatment of cancer has advanced significantly with single-target therapy, albeit it has drawbacks. Multi-target therapy is an

alternate tactic that uses polypharmacological medications or drug combinations when single-target therapy is ineffective [42].

8. It is difficult and expensive to discover novel pharmaceutical anti-cancer medical science; therefore, it is pivotal to find more practical and affordable approaches [43].
9. Researchers have been studying this ring system for decades because to the coumarins' remarkable bioactivity and extensive distribution. Among their various biological actions are growth regulation, illness prevention, and antioxidant qualities. According to scientific research, these substances exhibit anticancer effects based on how they affect immune modulation, cell proliferation, and differentiation. Due to their hepatotoxic effects, the majority of natural coumarins are not widely used; nonetheless, molecular alterations have produced comparatively safe counterparts with greater potency.
10. In terms of anticancer activity, saponins have a number of benefits, but they also have certain drawbacks. It is also challenging to acquire steroidal saponins from plants with complex structures due to their low content and limited bioavailability > 10%. Steroid saponins potential for further clinical use is restricted by all of these considerations [44].
11. The selective autophagy modulators that are currently on the market have poor bioavailability because of drawbacks such low solubility in aqueous media, untargeted distribution, toxicity, and resistance linked to higher drug doses. Additionally, their employment in practice settings is limited [45].
12. Regretfully, several research has indicated that celastrol may result in a number of adverse consequences, including renal, hematological, hepato, cardiac, and reproductive damage. Celastrol specifically inhibits CYP_3A_2 in a mixed manner in addition to being a competitive prohibition of CYP_2C_{11} and CYP_1A_2. Because celastrol may alter coupled drug break down enzymes, worsen noxiousness and adverse consequences, this further implies that we should be more watchful for potential interactions with other medications in the future [46].
13. There are several obstacles in the way of finding natural anti-cancer drugs, which delays the creation of efficient cures. These natural compounds complex molecular makeups present several difficulties, making their separation, identification, and synthesis challenging and resource-intensive. Furthermore, poor absorption and dispersion in the body limit the effectiveness of natural substances as anti-cancer medications, raising questions regarding their bioavailability [47]. Since some natural compounds can be dangerous, toxicity is an important factor that requires careful toxicological research to guarantee patient safety. Furthermore, over time, cancer cells may develop resistance to medicines made from natural sources. Thus, a better comprehension of resistance instruments along with synthesizing fresh tactics in order to overcome this resistor are crucial [48].

4. Future Perspectives

Triazole-containing coumarins have drawn a lot of interest from researchers and are frequently employed as anticancer scaffolds. The triazole moiety increases binding affinity to enzymes and receptors and promotes improved solubility. Triazolyl-coumarin-based fluorescent probes were created to assess cytotoxicity against cervical too breast adenocarcinoma cells in order to get fine biological reactivity.

The targeting and hazard analysis of metallic anticancer medications are greatly enhanced by green biomaterials, which use sustainable and biocompatible materials while lowering toxicity. Researchers can develop sustainable drug distribution methods with targeted delivery, regulated release, and decreased blood poisoning by combining natural polymers or biodegradable nanoparticles [49].

Heterocyclic derivatives containing sulfur have been shown to bind with a variety of protein targets particular to cancer. Benzothiazole, thiazole, thiophene, thiazolidinedione, benzothiophene, phenothiazine, and other intriguing derivatives of sulfur-containing heterocyclics have been demonstrated to block a variety of signaling pathways linked to cancer. Due to possible binding interactions inside the ATP pocket, significant advancements have also been made in molecular targeted therapy against particular enzymes, such as kinase receptors [50].

The intricacy of tumors in patients and the physiological factors influencing both intrinsic and acquired treatment responses cannot be accurately replicated by any preclinical model. To obtain the most useful data on therapeutic responses in tumors, drug metabolism, pharmacodynamic biomarkers, etc., before clinical translation, it is therefore ideal to employ a combination of models [51]. Patient derived explants culture methods have been shown to be clinically predictive, but not extensively used in designing new cancer pharmaceuticals. PDEs ought to be revived respecting potent diagnosis platform for producing proof-of-concept data. This might lower high turnover rate presently seen in cytotoxic clinical trials by giving PDEs a solid justification for continuing or stopping a chemical [52].

A promising new field of research in the fight against cancer is nitrogen-containing heterocycles. These compounds have the potential to be at the forefront of innovative treatment approaches in overcoming the complex challenges presented by cancer by leveraging their inherent properties and collaborative scientific research [53].

Quinones development as targeted chemicals for cancer treatment holds promise for the use of customized medicine in the future. By taking use of quinones special qualities and their capacity to interact with particular molecular targets or pathways, tailored treatment plans can be developed to improve patient outcomes and lessen side effects [54]. All things considered, research on quinones is crucial to the creation of potent and specific anticancer drugs. The future of quinone-based molecules for targeted cancer therapy will surely be influenced by ongoing research into innovative strategies, interdisciplinary partnerships, and advancements in pharmaceutical chemistry. Before being approved for use in patients, phytochemical anticancer medicines must first demonstrate a high level of efficacy through sufficient clinical trials.

The main issues with using phytochemical substances to treat cancer remain their low water solubility, shallow reach into primary cells, imbibing by typical units, limited curative potential, with harmful secondary effects [55]. For instance, because of their adverse effects, drugs such as colcrys, D-camptothecin, moreover variants of Podofilox possess narrow utility [56]. Therefore, it is anticipated that new developments in analytical technology and computational approaches will make it easier to identify novel phytochemicals, maximize their extraction, and/or choose to chemically synthesize or modify them [57].

In order to identify new and more successful cancer treatments, targeting therapy has been the main focus of treatment in recent decades. Monotherapy was the first to be utilized, followed by combination therapies, and multi-targeted therapy was launched in recent years [58]. The deployment of small molecules is the main focus of the multi-targeted agents now in use. Because of their high binding affinities, selectivity, specificity, and effectiveness.

In oncology, Dibenzocyclooctadiene lignans (DBCLS) belonging to genus Schisandra have created latest opportunities for plague prevention and treatment. Although DBCLS are known for a variety of biological activities, they are mostly linked to cell cycle disruption, apoptosis induction, and improving the efficacy of currently available cytotoxic medications. DBCLS are positioned as attractive options for upcoming oncological applications because of their promising potential [59]. For DBCLS, the transition from laboratory to clinic is still crucial. Although DBCLS is known to induce apoptosis, it is imperative to broaden research to examine its impacts on additional modes, such as gangrene, anoikis, oxytosis, and pyroptosis, as this can offer comprehensive knowledge of DBCLS anticancer properties. More accurate and focused cancer treatments may result from this understanding [60].

It has been demonstrated that the natural paclitaxel extracted from Taxus species is both commercially and biodegradable unprovable, despite the drug's numerous clinical achievements. Because of this, scientists are always trying to come up with new ways to satisfy the need for this medication in society. Paclitaxel can now be obtained by various techniques, as substance and cell culture, chemical synthesis, microbial fermentation, and artificial cultivation [61]. Furthermore, there are major restrictions on the clinical use of paclitaxel due to its limited water solubility. Serious side effects may result from the use of Cremophor EL with ethanol in conventional paclitaxel formulations. A number of novel paclitaxel dosage forms based on nanotechnology have been created in recent decades, such as liposome-encapsulated taxol, nant-paclitaxel, albumin-bound onxol, and polymer- abraxane couples. These ultrafine particles can considerably increase paclitaxel's antitumor efficacy while also lowering its toxicity [62].

5. CONCLUSIONS

This review focuses on the design and synthesis strategies of pyrimidoquinoline derivatives as promising novel anticancer agents. It provides a comprehensive overview of recent advances in synthetic methodologies used to construct the pyrimidoquinoline scaffold, along with key structural modifications that significantly influence their biological activity. The study show structure activity relationship insights, highlighting how different functional substitutions can enhance anticancer potency and selectivity toward cancer cells. Furthermore, this review critically evaluates the anticancer activities of these derivatives through various *in vitro* and *in vivo* biological analyses, including cytotoxicity studies against multiple cancer cell lines. Several compounds within this class state notable efficacy, suggesting their potential as lead molecules in anticancer drug development. In addition, the review discusses mechanistic pathways involved in their anticancer effects, such as apoptosis induction, cell cycle arrest, and inhibition of key molecular targets associated with tumor progression. Finally, it outlines future prospects for optimizing pyrimidoquinoline based compounds, focusing on improving pharmacokinetic properties, reducing toxicity, and enhancing target specificity, thereby supporting their advancement as next-generation anticancer therapeutics.

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Author's contribution:

Muhammad Javid: Conceptualization, Formal analysis, Investigation, Supervision, Validation, Writing-original draft. Sabahat Asghar: Data curation, Formal analysis, Investigation, Validation, Writing-review & editing. Muhammad Sagheer: Investigation, Writing-review & editing. Sumera Rani: Formal analysis, Investigation, Investigation, Writing-original draft, Validation, Formal analysis. Muhammad Sajid Abass: Conceptualization, Investigation, Writing-review & editing. Ihsan Maseeh: Validation, Formal analysis, funding acquisition. Muhammad Hasnain: Conceptualization, Project administration, Funding acquisition, Supervision. Farah Yaqoob: Investigation, Writing-original draft, Writing-review & editing.

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