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Review Article

Imidazo[1,2-a]pyridineBasedCompounds:TheHopefulAnti-Cancer Therapy

Akram M.H. Altaher[1*], Mohammed A. Adris[2], Saeb H. Aliwaini[3]

[1]Faculty of Postgraduate Studies and Scientific Research, University of AL-Butana, Ruffaa, Sudan
[2]Departmentof Biochemistry, University of AL-Butana, Ruffaa, Sudan
[3]Department of Biological Sciences and Biotechnology, Islamic University of Gaza, Palestine

ABSTRACT

Chemotherapy is a type of cancer treatment that uses a systemic drug to kill cancer cells wherever it finds in the body. It implements their actions through intervention with molecular mechanisms such as some core regulatory enzymes, molecular processes, or immune-related pathways during cell division and proliferation. Imidazo[1,2-a]pyridines (IPs) are nitrogen-based heterocycles that have a wide variety of biological activities. This review highlights the anticancer properties of chemotherapy and the problems facing it as an anticancer therapy, Furthermore, it reviews the available works of literature focused on the potential efficacy of IPs-based compounds in cancer treatment, and discuss the molecular mechanisms driving its anticancer effects; through clarification the targets associated with cancer. This review also will benefit the research community in the field of anticancer agent discovery by introducing the IPs as novel therapeutic agents. Various In-vitro studies have shown different IPs -based compounds have potential therapeutic effects against different cancer cell lines including; breast, liver, colon, cervical, lung, and kidney cancers. The anticancer effects of these compounds primarily result from their inhibitory effects on different molecular mechanisms including, PI3K/Akt, CENP-E, IGF-1R, CDKs, Tubulin Polymerization Inhibition, and c-Met inhibition.

Keywords: Imidazo[1,2-a]pyridine Compounds, Anti-Cancer, Anti-Proliferative activity, Apoptosis, Cell cycle arrest, Autophagy.

Correspondence:

Akram M.H. Altaher, Faculty of Postgraduate Studies and Scientific Research, University of AL-Butana, Ruffaa, Sudan, E-mail: a.taher@ucst.edu.ps

INTRODUCTION

Cancer is a common term for a broad cluster of diseases that really can affect any organ of the human body (WHO, 2018). Cancer is the greatest threat against the means of life expectancy in this century worldwide (Bray F, *et al.*, 2018). Based on the most recent World Health Organization (WHO) reports in 2018, cancer is the second leading cause of death worldwide and about 9.6 million deaths in 2018 globally were due to cancer, where approximately 1 in 6 deaths was caused by cancer (WHO, 2018). The increase in the incidence of cancer in developing countries is due to the rising average lifespan, acceptance of western manner of living, and increased civilization (Benson JR, *et al.*, 2009). There are many ways to treat cancer including surgery, immunotherapy, hormonal therapy, radiation therapy, targeted treatment, stem cell transplant, and chemotherapy (NCI, 2021). The National Cancer Institute (NIH) stated that the type of treatment used is determined by the type of cancer and the nature of its progression (NCI, 2021). Some cancer patients have undergone one form of therapy, although others have undergone a mixture of therapies (Siegel RL, *et al.*, 2015). The word "chemotherapy" ("chemo") is referring to a type of cancer treatment that uses a systemic drug to kill cancer cells wherever it finds in the body (WHO, 2018). Imidazo[1,2-a]pyridines (IPs) are nitrogen-based heterocycles that have a wide variety of biological responses and are usually made with natural ingredients (DeSimone RW, *et al.*, 2004). IPs-based compounds have obtained considerable interest as possible anticancer therapeutics due to their potent inhibitory function against diverse cancers cells proliferation and migration (Kim YB, *et al.*, 2014). Many earlier In vitro studies have been shown IPs possess anti-cancer properties (Lee JH, *et al.*, 2013, Yun SM, *et al.*, 2013, Hieke M, *et al.*, 2012, A l m e i d a GM, *et al.*, 2018, Zheng X, *et al.*, 2013, Aliwaini S, *et al.*, 2019, Li GY, *et al.*, 2013). The objectives of this review paper are; i) to highlight the anticancer properties of chemotherapy and the problems facing it as an anticancer therapy, ii) to review the available works of literature focused on the potential efficacy of IPs compounds in cancer treatment, and discuss the molecular mechanisms driving its anticancer effects; through clarification the multiple receptors and targets associated with cancer.

Anticancer properties of chemotherapy

The majority of recent anticancer therapies have been seen to trigger the death of cancer cells by apoptosis (Galluzzi L, *et al.*, 2018). Alterations in the apoptotic pathways may determine tumor resistance to these therapies (Kolenko VM, *et al.*, 2000) The activation of the proteolytic pathways e.g. family of caspases enzymes is essential for the induction of cell death by apoptosis (Kolenko VM, *et al.*, 2000). Apoptosis is mainly conducted by two caspase-dependent pathways: the intrinsic pathway and the extrinsic pathway (Galluzzi L, *et al.*, 2018). Both pathways are based on a group of signaling pathways that control the process of apoptosis. However, cancer cells normally produce multiple mutations or changes to prevent apoptosis. Even when apoptosis has traditionally been considered the key mechanism of cell death caused by cancer chemotherapies, it has become evident that it may also cause autophagy, a degradation mechanism that is considered activated as a survival mechanism involving the recycling of cellular organelles and macromolecules that are triggered under stress conditions to encourage cell survival (Aliwaini S, *et al.*, 2016). However, there is a dispute as to whether the activation of autophagy increases or prevents cell death in response to chemotherapy agents (Bleloch JS, *et al.*, 2019). Anticancer effects of chemotherapy primarily result from their inhibitory effects on many molecular mechanisms such as; IGF-1R, PI3K/Akt, CENP-E, CDKs, etc. (Zhou J, *et al.*, 2018, Lee H, *et al.*, 2013, Al-Qatati A, *et al.*, 2017, Qian X, *et al.*, 2010, Byth KF, *et al.*, 2006).

The problems facing chemotherapies as an anticancer treatment

There are different types of chemotherapy drugs that are differentiated dependent on several aspects, such as their chemical structure, nature, mechanism of action, and their association with other therapies (Sudhakar A, 2009). Although, not all medications that are used to treat cancer act the same way (ACS, 2020). While chemotherapy is the most commonly used cancer treatment, it also has adverse side effects ranging from mild such as weight loss, feeling exhausted, appetite change, and the sense of fatigue to the extreme as nausea (Griffin AM, *et al.*, 1996), immunodeficiency (Crawford J, *et al.*, 1991), and harming normal body cells (Lin SR, *et al.*, 2017). Depending on the type of drug, the side effects of chemotherapy differ in patients and can also differ from one chemotherapy treatment period to the next. Most side effects, however, are not permanent, and many can be restrained or reduced (Galmarini D, *et al.*, 2012, Wade CA, *et al.*, 2018). Some chemotherapy medicines can cause receptor changes in tongue buds, sores of the mouth, and thinking and memory problems following chemotherapy called (chemo brain) (Wade CA, *et al.*, 2018). Another major problem facing chemotherapy is the tendency of cancer cells to produce a chemotherapeutic agent resistance mechanism that makes these drugs ineffective over time (Singh A, *et al.*, 2010). Unfortunately, despite the enormous efforts invested to treat cancers, there has been limited success because of the undesired side effects and drug resistance induced by the mentioned ways of treatments. In cancer treatment; drug resistance is one of the clinical challenges which usually results in cancer therapy failure or recurrence of cancer because of tumor cells being incompletely eliminated and this demands further studies to improve its treatments and to discover new chemotherapies (Komeili-Movahhed T, *et al.*, 2015). Drug resistance to cancer is a dynamic process influenced by alteration of the drug target, drug efflux, drug inactivation, DNA damage repair, inhibition of cell death, inherent cell heterogeneity, epigenetic effects, or any combination of these mechanisms (Zahreddine H, *et al.*, 2013). A critical aspect of modern cancer research is the quest for effective, safe, and selective anticancer compounds. New types of therapies without or with a little harmful effect are required to treat different types of cancer (Narsimha S, *et al.*, 2016).

Imidazo[1,2-A]pyridine compounds as hopeful candidate cancer therapy

IPs are of particular interest because they have diverse biological activities and are usually synthesized chemically from natural sources (DeSimone RW, *et al.*, 2004). These compounds have lately gained considerable interest as possible anticancer therapeutics due to their potent inhibitory function against diverse cancers cells proliferation and migration (Kim YB, *et al.*, 2014, Ducray R, *et al.*, 2011). Furthermore, many medicines contain IPs in their chemical composition used to treat different kinds of diseases e.g. ulcers, cardiac disorders, viral infection, fungal infection, bacterial infection, protozoal infection, etc. (Hieke M, *et al.*, 2012, Fisher MH, *et al.*, 1972, Gudmundsson KS, *et al.*, 2003, Ismail MA, *et al.*, 2004, Kaminski JJ, *et al.*, 1985, Ulloora S, *et al.*, 2013). Many researching works in the Previous have confirmed that IPs possess some anti-cancer activities (Lee JH, *et al.*, 2013, Yun SM, *et al.*, 2013, Hieke M, *et al.*, 2012, Almeida GM, *et al.*, 2018, Zheng X, *et al.*, 2013, Aliwaini S, *et al.*, 2019, Li GY, *et al.*, 2013). Despite a broad range of medicinal chemistry applications of imidazo[1,2-a]pyridine, no single IPs-based compound has been confirmed as a commercial drug against any types of cancers. IPs may be a useful scaffold bridge for researchers looking to investigate this versatile therapeutic bridge and develop promising anticancer agents based on imidazo[1,2-a]pyridines.

Imidazo[1,2-a]pyridines: The chemical compound

In the pharmaceutical industry, various heterocyclic substances play an important role where they have been formed as a bioactive bridge (Polshettiwar V, *et al.*, 2007). Approximately sixty percent of the most commercially available drugs contain one heterocyclic as a pharmacophore nucleus (McGrath NA, *et al.*, 2010). IPs are heterocycles containing a fused imidazole ring, formed from 5 to 6 heterocycles, have a variety of applications in the medicinal chemistry field because their synthesis is procced easily from chemical compounds available in nature (Shao T, *et al.*, 2017). IPs are considered to have antiproliferative activity according to many studies of the literature (Kim YB, *et al.*, 2014, Almeida GM, *et al.*, 2018, Lee H, *et al.*, 2012, Jung KH, *et al.*, 2013, Kim O, *et al.*, 2011, Lee H, *et al.*, 2013, Lacerda RB, *et al.*, 2014). IPs have also been named as nonbenzodiazepines because they are pharmacologically similar to benzodiazepines (Ismail MA, *et al.*, 2004). IPs are usually produced in situ from hydrazonoyl halides, 1,3-dipolar species that are extensively used 1,3-dipolar cycloaddition reactions or cyclo condensation reactions for the synthesis of different heterocyclic systems(Liu TC, *et al.*, 2016, Ferwanah A-RS, *et al.*, 2005). In recent years, many published studies have clarified the chemical methods used to synthesize IP compounds in the laboratory (Morjan RY, *et al.*, 2014, Thaher BAA, *et al.*, 2015, Thaher BAA, *et al.*, 2016). Examples of recent instances include; the synthesis of IPs compounds from the reaction of picoline derivatives 3, 4, 5, and 6 with hydrazonoyl chloride 1a in tetrahydrofuran in the presence of triethylamine at room temperature afforded IPs compounds 7, 8, 9, and 10, while the reaction of substituted picolines 3, 4, 5, and 6 with hydrazonylchloride 1b in the same conditions produced the expected IPs 11, 12, and 13 (Aliwaini S, *et al.*, 2019) (Figure 1).

Anticancer properties of Imidazo[1,2-A]pyridines compounds and their targets associated with cancer: Generally, The chemotherapies im-

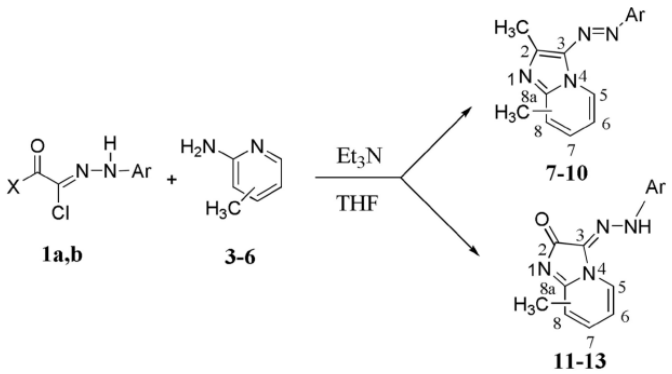

Figure 1 : IP compounds structures and synthesis (sources: Ref. [56]).

plement their action through affecting or direct intervention with molecular mechanisms such as some metabolic intermediates, core regulatory enzymes, molecular processes, or immune-related pathways during cell division and proliferation. In the following parts of this review paper, the anticancer properties of IPs-based compounds and their multiple targets associated with cancer are discussed, with particular emphasis on the experimental studies that have explored the molecular processes of IPs anticancer abilities against cancer cell lines In-vitro.

Phosphoinositide-3-Kinase (Pi3k) and Akt Inhibition

Angiogenesis is essential for tumor growth, invasion, and metastasis. The PI3K/Akt is a signaling pathway that governs different mechanisms in the living cell such as its anabolism, catabolism, cell cycle improvement, caspases dependent apoptosis, and rearrangement of cytoskeleton spindles and it phosphorylates more than 20 endogenous substrates (Kim YB *et al.*, 2014). Further, it plays a significant role in angiogenesis, and this pathway inhibition contributes to antiangiogenic activity against the lines of cancer cells. Numerous in vitro studies reported that IPs-based compounds (e.g. IP-Se-05; P-Se-06; HS-104; HS-106; HS-173; IPD-196; IP-6) can cause inhibitory effects against cancer cells proliferation, at relatively low concentrations, where they have potent dual inhibition against PI3K/Akt/mTOR signaling pathway. According to these studies, IPs-based compounds as a monotherapy exhibited antiproliferative effects against many cell lines (such as; Breast cancer, Human hepatocellular carcinoma, Liver cancer, Lung cancer, Melanoma, HeLa cervical cancer) with IC50 values ranging from 0.01 to 44.6 μM (Table 1). The lowest cytotoxicity was recorded by Jung, *et al.* who found that IP-based compound (HS-104) had a promising activity against hepatocellular carcinoma cells (HCC) with cytotoxicity IC50 = 0.01 μM. According to mostpreviousstudies, exposure of IPs-based compounds resulted in a significant increase in the number of cells in the G2/M phase, and a decrease of its number in the G0/G1 phase, which resulted in delaying the progression of the cell cycle (cell cycle arrest), which was confirmed by decreased the expression of cyclin B1 and increase the expression levels of p-cdc2 and p-cdc25. Furthermore, the percentage of arrested cells was significantly higher with the combined treatment than the percentage of the cells treated with IPs-based compounds alone. Based on these studies, it is reasonable to suggest that IPs-based compounds exhibit inhibition of cell proliferation by inducing cell cycle arrest at G2/M phases. On the other hand, IPs-based compounds have been found to trigger apoptosis in a wide variety of cancer cells including breast, human hepatocellular carcinoma, liver, lung, Melanoma, cervical cancer cells (Antonopoulos AS, *et al.*, 2012). However, the apoptotic effect of IPs-based compounds in a variety of cancer cells was confirmed by an increase in PARP cleavage in cells treated with IPs-based compounds as compared to control cells. Also, the increased levels of Bax and cleaved caspases 3, and 9 and decreased the expression of Bcl-2 in a dose-dependent manner. Overall, this indicated IPs-based compounds cause apoptosis of cancer cells by influencing the mitochondria and induction of caspases.

Centromere-Associated Proteine (cenp-e) inhibition

Centromere-associated protein E (CENP-E) is a mitotic spindle motor protein undergo to the superfamily of kinesin, and contains an ATPase domain in its motor region. It is the primary receptor responsible for mitotic checkpoint signal transduction after connection with spindle microtubules. Inhibition of CENP-E offers a novel strategy for anticancer agents because the loss of CENP-E function causes failure of metaphase chromosome alignment and induced cell cycle arrest and apoptosis (Wood KW, *et al.*, 2010, Hirayama T, *et al.*, 2013). Three studies have reported that two Imidazo[1,2-a] pyridine-based compounds (GSK923295 and 5-Bromo-2,3-disubstituted Imidazo[1,2-a]pyridine) inhibit the proliferation of human hematological cell lines, breast cancer, colon cancer, and cervical cancer cell lines with IC50 concentrations ranging from < 0.003 to 44.6 μM (Table 2). These compounds induce cell cycle arrest leading to apoptosis and cell death. That is due to its highly potent and selectively inhibition for CENP-E kinesin motor ATPase activity (Wood KW, *et al.*, 2010, Hirayama T, *et al.*, 2013).

Table 1: Studies on the anticancer effects of IPs-based compounds that reported PI3K/Akt inhibition as a target associated with cancer

Targets associated with cancer	Type of Cancer Cell Lines	Effective Concentration (μm)	Monotherapy/ Combination	Reference
PI3K/Akt Inhibition	Breast cancer	1.1 – 4.8	Monotherapy	48
	Hepatocellular carcinoma cells (HCC)	0.01 – 10.0	Monotherapy	49
	Breast cancer	0.6 – 7.8	Monotherapy	50
	Liver cancer & Breast cancer	0.1 – 10.0	Monotherapy	51
	Lung cancer	0.9 – 10.0	Monotherapy	22
	Breast cancer	0.1 – 10.0	Monotherapy	15
	Melanoma & HeLa cervical cancer	9.7 – 44.6	Monotherapy	14
	HCC	2.61 – 4.41	Monotherapy	9
	Human breast carcinoma	12.5 – 26.0	Monotherapy	12

Table 2: Studies on the anticancer effects of IPs-based compounds that reported inhibition of CENP-E, IGF-1R, CDK, Tubulin Polymerization and, c-Met as a target associated with cancer

Targets associated with cancer	Type of Cancer Cell Lines	Effective Concentration (µm)	Monotherapy/ Combination	Reference
CENP-E Inhibition	Hematological cell lines	<0.003	Monotherapy	24
	Breast cancer, Colon cancer	0.012-10.0	Monotherapy	60
	Cervical cancer	0.05	Monotherapy	61
IGF-1R Inhibition	Multiple myeloma, Lung carcinoma	0.005-0.104	Monotherapy	64
	HCC	0.003-1.26	Monotherapy	66
CDK Inhibition	Human colon carcinoma	5.5	Monotherapy	68
	Breast cancer	0.07-0.6	Monotherapy	69
	Breast cancer, Ovarian, Prostate, Lung, Colon, and Cervical	0.2-2.1	Monotherapy	25
Tubulin Polymerization Inhibition	Kidney cancer	5-8	Monotherapy	73
c-Met Inhibition	Human lung cancer, kidney cancer, lung cancer, gastric *carcinoma*, prostate cancer	1.5-20	Monotherapy	53
	Human lung cancer	0.8-54.3	Monotherapy	74

Insulin-like growth factor-1 receptor inhibition

Insulin-Like Growth Factor-1 Receptor (IGF-1R) is an element of the large class tyrosine kinases receptors, belongs to the insulin receptor family, found on the surface of human cells, and (Gregory CW, *et al.*, 2001). It is a transmembrane receptor that plays an important role in several critical signaling cascades. By activating both the PI3K/Akt and Ras/Raf/MAPK pathways, IGF-1R is a key element in the proliferation, transformation, and metastasis of cancer cells (Hartog H, *et al.*, 2007). Two studies demonstrated that IPs compounds treatment as monotherapy at concentrations of 0.003-1.26 µM induced significant anti-proliferative effects in cancer cells e.g. multiple myeloma and lung carcinoma by inhibition of IGF-1R (Emmitte KA, *et al.*, 2009, Ducray R, *et al.*, 2011). One of these studies demonstrated the ability of IPs compounds (IC50= 0.005 µm) to inhibit the proliferation of multiple myeloma (Emmitte KA, *et al.*, 2009). Furthermore, when compared to tumor cell lines, IPs compounds demonstrated superior selectivity against normal HFF cell lines (Ducray R, *et al.*, 2011). Ducray *et al.* reported that IPs compounds at a concentration of 0.003-1.26 µM were found to be an IGF-1R inhibitor and promising novel treatment for cancer because they work by interfering with the cell cycle to further increase the selectivity and causing cancer cells death by apoptosis (Ducray R, *et al.*, 2011) (Table 2).

Cyclin-Dependent Kinase inhibition

Cyclin-Dependent Kinase (CDK) are protein kinases and work competitively with ATP to catalyzing the regulatory proteins of the cell cycle. They also play a role in controlling the transcription and processing of mRNA (Morgan DO, 2007). Cdks phosphorylation triggers sequential intramolecular interactions that progressively block Rb functions as cells move through G1 phase which induces apoptosis (Hamdouchi C, *et al.*, 2005, Byth KF, *et al.*, 2004). Agents that inhibit CDKs are a novel strategy for cancer treatment. As a result, IPs compounds have been developed as a potent inhibitor of CDKs in cancer cells (Cai D, *et al.*, 2006). Three in vitro studies have demonstrated that IPs-based compounds as monotherapy have antiproliferative activity against various cancer cell lines (such as; human colon carcinoma, breast cancer, ovarian, prostate, lung, colon, and Cervical) at concentrations of 0.05-5.5 µm (Table 2) (Hamdouchi C, *et al.*, 2005, Byth KF, *et al.*, 2004). These studies reported that treatment of tumor cells with IP-based molecules resulted in cell cycle arrest in G2/M phase and blockage of DNA synthesis in the S phase causing cell death by apoptosis (Hamdouchi C, *et al.*, 2005, Byth KF, *et al.*, 2004).

Tubulin polymerization inhibition

Microtubules are a principal and dynamic component of cytoskeletal consisted of α,β-tubulin heterodimer assembly (Etienne-Manneville S, 2010). Due to its dynamic structures that undergo continual assembly and disassembly within the cell; The function of microtubules filaments is an organization of the cell shape during its movements, including some kinds of cellular locomotion, intracellular transportation, and the chromosome's separation during cell division (Cooper GM, 2000). Antitubulin agents have become an attractive target for anticancer therapy. One in vitro study has reported that three IPs-based compounds as monotherapy have antiproliferative activity against kidney cancer cell lines at concentrations of 5-8 µm, where it exerts its action by disrupt tubulin-microtubule dynamics causing cell cycle arrest and eventually cell death by apoptosis (Table 2) (Sanghai N, *et al.*, 2014). Treatment of kidney cancer cells with the three IPs-based compounds induced caspase 3-depended apoptosis through the arrest of the cell cycle in G2/M phase. Furthermore, IPs-based compounds also prevented tubulin polymerization and also disturbed the tubulin-microtubule complex.

Hepatocyte growth factor receptor inhibition

The Hepatocyte Growth Factor Receptor (HGFR), also known as c-Met, is an oncogenic fusion pro¬tein and it belongs to the subfamilyof Receptor Tyrosine Kinases (RTKs), RTKs play an important role in the growth and progression of different types of cancer. c-Met activation is regulated by binding with its natural ligand, HGFR, and interac-

tion with other membrane receptors (Li C, *et al.*, 2015). The common functions of HGF/c-Met pathway are usually limited to embryogenesis, repair of injured tissue in adults (Porter J, 2010). Different types of cancers have been associated with abnormal stimulation of the HGF/c-Met pathway because it can trigger cell proliferation, migration, invasion, and avoidance of apoptosis, leading to tumor formation, angiogenesis, and metastasis. Also, c-Met overactivation leading to drug resistance (Engelman JA, *et al.*, 2007). For these reasons, c-Met dysregulation agents provide a novel approach for anticancer therapy. Two in vitro studies published that Imidazo[1,2-a]pyridine-based compounds have an anti-proliferative effect at relatively low concentrations where they have dose-dependently inhibition against the phosphorylation of c-Met and its main downstream PI3K/Akt and ERK signaling pathways. According to these studies, many IP-based compounds as monotherapy have anti-proliferative effect against various cell lines (such as; kidney cancer, Lung cancer, gastric carcinoma, prostate cancer) with concentrations from 0.8 to 54.3 μM (Table 2).

CONCLUSION AND FUTURE PERSPECTIVE

Imidazo[1,2-a]pyridine compounds have many clinical applications where differents drugs containing IPs compounds are currently used to treat various diseases e.g. ulcers, insomnia, heart disease, and different microbial infections e.g. viral infections, bacterial infections, and fungal infections. During the last two decades, efforts have been devoted to clarifying the possible anticancer activities of IPs-based compounds against various types of cancer cell lines including; breast, liver, colon, cervical, lung, and kidney cancers. However, several in vitro experimental observations have shown that anticancer effects of these compounds primarily result from their inhibitory effects on six main molecular mechanisms: i) PI3K/Akt, ii) CENP-E, iii) IGF-1R, iv) CDKs, v) Tubulin Polymerization Inhibition, and vi) c-Met inhibition. According to these studies, it is acceptable to suggest that IPs-based compounds exhibit their anti-proliferative effects on various cancer cell lines by inducing cell cycle arrest at G2/M phases, partial blockage of DNA replication in S phase, highly potent and selectively inhibition for CENP-E kinesin motor ATPase activity, affecting the mitochondria, and activating caspases, prevented tubulin polymerization, and also disturbed the tubulin-microtubule complex which resulted in cell death by apoptosis. Despite the promising findings from basic and preclinical investigations, the results of clinical trials are very limited. Therefore, further clinical studies are needed to determine whether IPs-based compounds have similar effects as in culture and which subtypes of cancer patients may benefit from IPs-based compounds treatment. Also, more investigations are required to determine meaningful approaches of IPs compounds administration, such as the enhancement of IPs compounds effects in combination with specific chemotherapy or radiotherapy. In conclusion, the current evidence indicates that IPs-based compounds will play an important role in the future management and prevention of different cancers.

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