REVIEW ARTICLE

Hybrid Compounds as Multitarget Directed Anticancer Agents

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Abstract: Cancer is a multifactorial disease including interactions of complex genetic and environmental factors. Clinical efficacy of anticancer chemotherapies is hampered by various factors including multidrug resistance (MDR). There is a strong need to discover more potent novel cancer drugs to kill cancer cells selectively. The recent new strategy for cancer treatment involves the design and synthesis of hybrid compounds as multitargeted anticancer agents. In this review, we focus on studies using hybrid compounds which were designed and synthesized from two or more different bioactive moieties conjugating them into a single hybrid drug. Hybrid compounds having more than a single target have been considered as more efficient and potent anticancer agents, since it is almost impossible to destroy cancer cells with a single target. Hybrid compounds overcome many disadvantages of single cancer drugs such as low solubility, adverse effects, and multi drug resistance. We have compiled the data of recent studies using the new hybrid anticancer drugs in cancer treatment. Thus, the design, synthesis and clinical trials of new hybrid compounds should be continued and supported in future. Results of recent studies have proved that they have a great potential to be used as novel anticancer drugs.

Keywords: Hybrid Compounds, Cancer, Anticancer Agents, Multitarget Compounds, Drug Design, Natural Products.

1. INTRODUCTION

Cancer is abnormal growth of cells, which can overspread to normal cells of the body. Cancer has serious consequences in health, leading to death if not treated. According to the World Health Organization (WHO) worldwide, 14.1 million patients were diagnosed newly having cancer. Furthermore, 32.6 million patients were living with cancer and deaths from cancer were 8.2 million in 2012. In the next two decades, the number of new cancer patients is expected to increase around 70%. The main target of cancer therapy is to relieve patients completely from the disease and to increase the lifespan and life quality of the patients. Since cancer has various properties depending on its localization, cause and stage. Because of the type and properties of cancer, cancer therapy is very complex and differs markedly. Therefore, it is not a single type of disease. Chemotherapy is usually an important treatment approach in many cancer cases. Unfortunately, most of the cancer cells develop resistance to several drugs used in treating cancer. Hence, increasing the drug sensitivity through elimination of drug resistance is crucial step for the successful treatment of cancer patients.

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For a long time, various approaches such as drug combination, traditional or new synthesized drug have been investigated to cope with this difficult problem. At the cellular level is low bioavailability of drug combinations, moreover it is seen that similar mechanism of developing against new synthesized drug. There is an intensive ongoing research to develop more efficient treatment strategies in the fight against cancer. Recently, it has been developed a different perspective on the new drug design. The principal of this new angle of view bases on different functions to provide in single molecule. Therefore, new synthesized molecule has not only one target but also multiple targets. In this way, new design drugs have an anticancer activity increased sensitivity compared to its previous form. On the other hand, it may decrease risk of developing drug resistance. Additionally, it may have pharmacokinetic features and avoiding adverse effects to normal cells. Because of these features, researchers carefully keep abreast of the design of hybrid compounds in latest developments cancer therapy. Thus, this review focuses on hybrid compounds as new promising anticancer drugs in cancer therapy.

2. HYBRID COMPOUNDS

The development of effective drugs to treat cancer continues to be the major interest of the researchers in the world. It is now a common opinion of the researchers that a complex disease such as cancer cannot be treated with a single

drug. Therefore, hybrid compounds having multiple targets and acting on different mechanisms need to be applied instead of a combination of drugs. It has led to the idea and development of hybrid drugs having different targets which is a very popular subject to be used in cancer therapy nowadays. Hybrid multi-target compounds consist of two drug substances into a single molecule, and the new synthetic hybrid compound is more medically effective than its individual components, directly or its metabolic products [1]. Hybrid compounds have two or more bioactive sites, and act on different mechanisms in cancer cells. Hybrid compounds are classically described as chemical individuals combining at least two pharmacophores through a covalent bond [2]. A successful hybridization process is realized without losing the natural chemical properties of the two individual drugs [3]. Generally, two pharmacophores can be directly linked by a stable covalent bond (e.g., amine, amide) or through a linker which may also add a specific solubilizing function to the final compound. While molecular designing new hybrid compounds, it should be taken into account most ideal their pharmacodynamics conditions. Hybrid molecules are larger than the two individual consisting drugs, and usually more lipophilic. Therefore, the solubilizing linker is needed to be as basic as possible [4].

3. HYBRID COMPOUNDS IN CANCER THERAPY

Cancer is hugely complex multi-factorial and multigenetic disease, and many researchers from various disciplines have still working to find a cure. Combination therapy that combines multiple drugs working on different mechanisms is a proven therapeutic strategy for disease management. The recent clinical trials on the concurrent use of different anticancer drugs have been suspended due to the high toxicity and adverse effects of the different drugs. The recent studies have proven that the hybrid chemotherapeutic agents have more beneficial effects and fewer side effects than single agents via simultaneously modulating multiple targets and circumventing differences in pharmacokinetic profiles.

The advantages of hybrid molecules can be stated as follows compared to the combination of multiple drugs: (1) the ideal timing window and enhanced synergistic potential are achieved by hybrid molecules in comparison to the concurrent use of separate agents; (2) diminished risk of developing drug resistance; and (3) enhanced pharmacokinetic features and decreased toxic adverse effects compared to the administration of multiple agents. In addition to these advantages, hybrid compounds may improve patient compliance to treatment and reduce cost of treatment.

3.1. Hybrid Compounds Having Antioxidant in the Structure

Recent studies demonstrated a tight relation between cancer and oxidative stress. Cancer itself produces intrinsic oxidative stress involving production of reactive oxygen species (ROS). ROS are important mediators regulating signal transduction [5]. Intrinsic ROS production in cancer cells are more than normal cells and increasing oxidative damage in cancer cells is a new therapeutic strategy. The cinnamaldehyde generates ROS, but the clinical applications of cinnemaldehyde have limited since its poor bioavailability. Thus, quinone methide-cinnamaldehyde (QCA) is a recently designed hybrid anticancer drug (**a**, Fig. **1**). This hybrid design has provided synergistic manner to exaggerate oxidative stress. In vitro and in vivo models demonstrated that H_2O_2 and acidic pH caused QCA to release quinone methide and cinnemaldehyde, respectively, leading to the death of cancer cells. Thus, the strategy of the new hybrid compound has disrupted redox balance to hit cancer cells more specifically and effectively [6].

Zinc, copper, manganese and selenium are trace elements and have been demonstrated to protect normal cells from the damages caused by chemotherapeutics, while having a weak protection on cancer cells. Trace elements are necessary for the activities of the key antioxidant enzymes such as Cu/Zn superoxide dismutase (Cu/Zn-SOD), manganese superoxide dismutase (Mn-SOD), and glutathione peroxidase (GPx). The key antioxidant enzymes play critical role in the ROS level. Trace elements were shown to have a negative effect on chemotherapeutic sensitivity. Trace elements were found significantly lower in cancer tissues adjacent to the non-cancer liver tissues. The level of trace elements were reported to correlate negatively with the drug resistance [7]. Radical scavenging and cytotoxic activities of thirty new hybrid selenocarbamates were studied in a recent in vitro study using a panel of human cell lines. Among the synthetic selenium compounds, Selenocyanate and diselenide hybrid derivatives containing a carbamate component were studied mostly and found to exert cytotoxic and radical scavenging activities in several cancer cells [8]. Selenocyanate was found effective in the prevention and treatment of cancer in several studies. Selenocyanate was reported to involve prevention of mechanistic target of rapamycin (mTOR) signaling [9], tubulin polymerization [10] nitric oxide levels [11], and modulation of antioxidative enzymes. Diselenide compounds defend against oxidative stress acting as antioxidant in cancer. Some diselenide agents mimicked the peroxidase activity of selenium based glutathione peroxidases. Analysis of the bioavailability and toxicity of some hybrid compounds evaluated as a nontoxic compound with drug-likeness features. On the other hand, some diselenide compounds were cytotoxic and induced apoptosis with inhibition both tubulin polymerization and Akt signaling pathway in various cancer cells [10-13].

Oxidative stress generated by some chemotherapeutic agents has been reported to induce apoptosis leading to DNA damage and cell death in cancer cells in several studies [5, 14-33]. Piperlongumine (PL) is a natural agent which has been reported to kill cancer cells via inducing oxidative stress and apoptosis while protecting normal cells in vitro and in vivo studies [34]. Mechanism of action of 80 piperlongumine analogs synthesized modifying each carbon atom was examined in in vitro models of cancer. The c2-c3 olefin in PL is important for increasing the levels of ROS. Because of chemical structures of PL and associated with its compounds are multivalent electrophilicity, they can benefit cancer-selective toxicity [35]. In another study, a new hybrid compound was synthesized by arylation of piperlongumine at C-7 position with a combretastatin-A4 (CA4) which mimics an antimicrotubule agent (**b**, Fig. **1**) [36]. CA4 binds to tubulin, prevents its polymerization and exerts cytotoxic effects in various human cancer cell lines [37]. Due to the low

solubility of CA4, its clinical application is restricted. KSS-9 is one of the several new synthesized hybrid compounds having potent antiproliferative effects in eight cancer cell lines. KSS-9 was reported to induce ROS generation and protein glutathionylation in cancer cells. In addition, it impaired the tubulin polymerization and caused a potent G_2/M cell cycle block [36].

Nitric oxide (NO) and ROS are the molecules targeted for the aim of discovering potential cancer therapy agents, many agents modulating NO pathways, and NO- and ROS-mediated signaling cascades are under investigation in several in vitro and in vivo studies [38]. O^2-(2,4-Dinitrophenyl) diazeniumdiolates generate diazeniumdiolates ions that automatically release NO under physiological conditions upon the nucleophilic attack of GSH and catalysis by glutathione S-transferases (GST) [39]. High NO concentration is cytotoxic leading to apoptotic cell death in cancer [40]. Oleanolic acid (OA) and its derivatives are cytotoxicity towards to various cancer cells, but their solubility is very poor. Thus, galactose with oleanolic acid hybridization increases solubility in aqueous. Oleanolic acid and galactose have shown synergetic effects to improve hepatic selectivity targeting hepatocellular carcinoma (HCC) [41, 42]. Galactosyl-(OA) conjugate and O^2-(2,4-Dinitrophenyl) diazeniumdiolate are two new anticancer hybrid compounds synthesized to achieve two main purpose of targeting cancer cells and creating cytotoxic effect on them. One new hybrid molecule was shown to induce apoptosis in HCC cells by arresting the cell cycle at the G_2/M phase, activating both apoptotic pathways and increasing the ROS level [43].

Extensive sun exposure has been considered to cause many acute and chronic skin diseases such as sun burns, photoimmune suppression, photoaging, and skin cancer. Effective and harmless photoprotectant agents need to protect people from long term side effects of sun exposure [44]. UV radiation causes a direct DNA damage through the formation of DNA adducts and/or ROS generation facilitating skin tumour [45]. Several antioxidants have been reported to inhibit ROS-induced DNA damage [46]. Because of chemoprotective properties; there is a great effort to develop new photoprotectors having antioxidant properties for the more efficient skin cancer therapy. In a study, new hybrid derivative compounds have been synthesized by molecular hybridization of *t*-resveratrol, avobenzone, and octyl methoxycinnamate. Antioxidant activity and photoprotection features of these new hybrid compounds have been evaluated and characterized, demonstrating that free radical scavenging and photoprotection activities of some hybrid compounds are more effective than *t*-resveratrol [47]. Thus, development of new hybrid compounds might be a promising be strategy for the treatment and prevention of skin cancer.

3.2. Hybrid Compounds Targeting the DNA of Cancer

Targeting DNA of cancer cells is widely accepted as an efficient treatment modality in the fight against cancer. Different chemotherapeutic agents exert their effects via targeting DNA in several types of cancer. 5- Fluorouracil (5-FU) has no activity if the cells are in G_0 or G_1 phase, but has cytotoxic activity if the cells are in S phase [48]. Several hybrid compounds of deoxypodophyllotoxin-5-fluorouracil were synthesized from naturally-occurring podophyllotoxin (PTT) and 5-FU. PTT has potent cytotoxic effects in many cancer cell lines [49]. The hybrid compounds showed less toxicity to the normal cells, but higher toxicity to the cancer cells in comparison to the toxic effects of the single use of anticancer drugs; etoposide and 5-FU. 4'-O-demethyl-4-deoxypodophyllotoxin-4'-yl4-((6-(2-(5-fluorouracil-yl) acetamido) hexyl) amino)-9-oxobutanoate is an efficient new hybrid compounds which was examined in this study. It induced cell-cycle arrest at G_2/M phase and prevented the migration of human lung cancer cells [50, 51].

Cisplatin (cisplatinum or cis diamminedichloroplatinum II) is a widely used chemotherapeutic agent for sarcomas, lymphomas, germ cell tumours, ovarian, lung, bladder, head and neck, and testicular cancers [52]. Currently, nine platinum analogs are under clinical trials all around the world. These are lobaplatin, enloplatin, ormaplatin (tetraplatin), oxaliplatin, 254-S, DWA2114R, JM-216,CI-973 (NK-121), and liposome-entrapped cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) (LNDDP) [53]. Cisplatin is a DNA alkylating agent [54, 55] and the most potent agent used for the treatment of ovarian cancer [55, 56]. Despite the potency of the platinum drugs in various types of cancer, drug resistance develops in many cancer types limiting their efficiency [56-58]. Dichloroacetate (DCA) was reported to change anaerobic glucose metabolism (glycolysis) to aerobic glucose oxidation in cancer cells and to decrease mitochondrial membrane potential. DCA induced mitochondrial apoptotic pathway leading to cancer cell death, while giving almost no damage to normal cells [59, 60]. Dichloroacetate-platinum (II) [DCA-Pt (II)] is a new hybrid platinum compound synthesized from dichloroacetate (DCA) and cisplatin, [DCA-Pt (II)] keeps both DCA and Pt in one molecule (**c**, Fig. **1**). It is more efficient in cancer prevention and to overcome cisplatin resistance. It induces apoptosis via movement of pyruvate into the mitochondria. Effects of DCA-Pt (II) on cell cycle (G_2/M phase) arrest and mitochondria-mediated apoptosis were investigated in cisplatin-sensitive (OC) and resistant (OCDDP) ovarian cancer cells. DCA-Pt (II) expanded the distribution of S phase by 35% and decreased the distribution of G_2/M by 11% in OC cells. The increase in the distribution of S phase was 18% and decrease in the distribution of G_2/M was ~11% in OCDDP cells. The results of this study demonstrated that DCA-Pt (II) induced G_2/M phase arrest in both resistant and sensitive ovarian cancer cells. Although DCA-Pt(II) induced intrinsic apoptosis in both resistant and sensitive ovarian cancer cells, its effect on mitochondrial apoptosis was more marked in the resistant ovarian cancer cells compared to the sensitive cells. These results prove that the DCA-Pt(II) is more efficient than other platinum drugs on mitochondrial apoptosis and cell cycle blockage [61].

Resveratrol (3,5,4'-tri-hydroxystilbene; RSV), is a polyphenolic antioxidant having cancer-preventing and anticancer properties [62]. Several in vivo and in vitro studies have demonstrated that RSV regulates intracellular signaling pathways related to apoptosis, angiogenesis, cellular growth, invasion, and metastasis [63-66]. RSV pertains to a class of chemicals called stilbenes. The members of stilbene family have features such as antioxidant, anti-inflammatory, and trigger apoptosis. They are different depending on the groups on the stilbene skeleton.

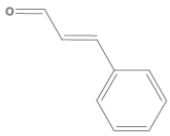
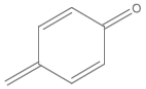
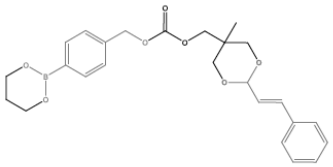
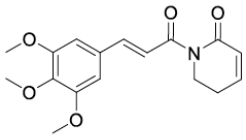
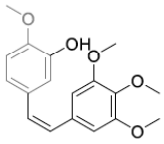
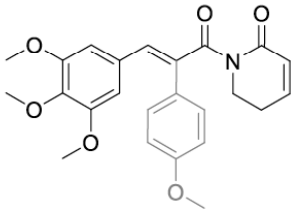
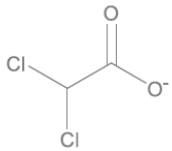
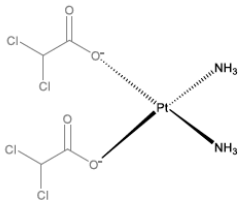
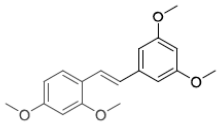
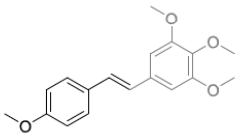
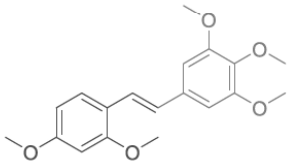
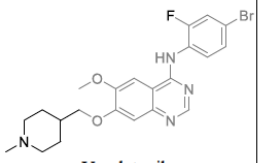
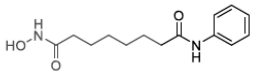
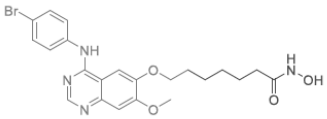
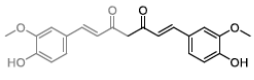
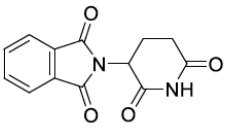
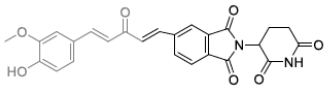
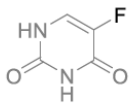
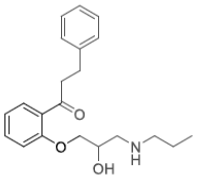
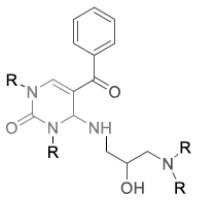
	Hybrid Component 1	Hybrid Component 2	Hybrid Structures	References
a	 Cinnamaldehyde	 Quinone methide		[6]
b	 Piperlongumine	 2-Methoxy-5-[(Z)-2-(3,4,5-trimethoxy-phenyl)-vinyl]-phenol		[36]
c	 Cisplatin	 Dichloroacetate		[61]
d	 2,3′,4,5′-tetramethoxy-*trans*-stilbene	 3,4,4′,5,-tetramethoxy-*trans*-stilbene		[69]
e	 Vandetanib	 Vorinostat		[88]
f	 Curcumin	 Thalidomide		[108]
g	 5-fluorouracil	 Propafenone		[131]

Fig. (1). Hybrid compounds and theirs components.

Methoxyl groups are responsible for apoptosis-inducing activity. Their antioxidant activity is determined by the position and number of hydroxyl groups on the benzene rings [67, 68]. Methoxylated stilbenes such as 3,4,4',5-tetramethoxy-trans-stilbene (MR-4) and 2,3',4,5'-tetramethoxy-trans-stilbene (TMS) are derivatives of RSV and have more potent anti-apoptotic activities than RSV. 2,3',4,4',5'-pentamethoxy-trans-stilbene (PMS) is a new hybrid compound synthesized from TMS and MR-4 (**d**, Fig. **1**). PMS induced apoptosis via activation of caspases, down-regulated PI3K/Akt signaling and enhanced polymerization of microtubules, which was followed by G_2/M phase cell cycle arrest. PMS was shown to have potent anti-mitogenic effect in three different colon cancer cells and prevented tumour growth in an experimental colon cancer [69].

3.3. Hybrid Compounds Containing HDACI

Histone acetylation and deacetylation are important determinants of gene expression two large enzyme families named as histone acetyltransferases (HATs) and histone deacetylases (HDACs) have opposite actions and govern acetylation process tightly. Histone acetylation induced by HATs associates with gene transcription. Acetylation is the most important epigenetic modification and key regulatory mechanism for gene expression and chromatin structure. In contrast, histone hypoacetylation induced by HDACs associates with gene silencing. Histone deacetylases (HDACs) are epigenetic enzymes which discard acetyl groups from N-acetyl lysine amino acids on histones leading to suppression and regulation of epigenetic gene expression. They regulate chromatin conformation, protein-DNA interaction, and transcription. Recently, HDACs have been demonstrated to deacetylate not only histones, but also some important regulatory proteins (e.g. p53, E2F, α-tubulin, and Hsp90) [70-74]. HDACs are implicated in several pathophysiologic states. Current studies have demonstrated that HDAC-inhibitors (HDACIs) inducing histone hyperacetylation are promising novel anti-cancer drugs in cancer treatment. HDACIs have been shown to have significant anticancer effects with negligible toxicity in the preclinical studies. Inhibition of HDACs enzymatic activity induced growth arrest and apoptosis in tumour cells. So far, four HDAC inhibitors (HDACI) have been approved by FDA. These are vorinostat (Suberoylanilide hydroxamic acid, SAHA) and romidepsin for the treatment of cutaneous T-cell lymphoma, and panobinostat for multiple myeloma. [75].

The formation of new blood vessels from the existing vessels is called angiogenesis which has an important role in tumour growth and metastasis. Several growth factors regulate angiogenesis. The growth factor X which was named later as vascular endothelial growth factor protein family (VEGF) and its receptors (VEGFR-1, VEGFR-2 and VEGFR-3) are the most important factors in angiogenesis [76]. These receptors are tyrosine kinase (RTK) receptors. VEGFR was reported to induce angiogenesis, cell growth and metastasis, reduce apoptosis, and alter cytoskeletal function a promising therapeutic strategy for cancer is to inhibit tumour growth and angiogenesis by targeting key growth factor receptors involving oncogenic tyrosine kinase signal transduction pathways. Receptor tyrosine kinases (RPTKs) have an important role in the development and progression of many cancers including ovarian, brain, breast, non-small cell lung cancers, etc. Most of the cancer patients do not respond to VEGFR targeted therapy. Combination therapies with multi-targeted tyrosine kinase inhibitors (TKIs) need to be developed and tested to overcome low responses and drug resistance. The c-Met is the hepatocyte growth factor (HGF) receptor and another tyrosine kinase receptor. Recent reports showed that c-Met/HGF and VEGFR/VEGF act synergistically in the progression of many cancers. Therefore, in many types of cancer, inhibition of VEGFR and c-Met receptor tyrosine kinases are considered as therapeutic targets. Studies have shown that a single target inhibitor does not provide the desired therapeutic effect. A single compound synthesized combining inhibitors of both VEGFR and c-Met which is able to inhibit both may enhance therapeutic efficiency of single inhibitors [77].

Current studies have shown that HDAC inhibitors have synergistic activity with RTK inhibitors, on suppression of cancer cell proliferation, inducing apoptosis and prevention of TKI resistance [78-82]. Several multi-targeted inhibitors against HDAC and RTK have been reported in the recent studies [83-86]. In contrast to dual inhibitors of HDAC and RTK, dual inhibitors targeting VEGFR and HDAC are not common [87]. N-phenylquinazolin-4-amine hybrids are a single agent synthesized combining inhibitors of VEGFR-2 (Vandetanib) and HDAC (Vorinostat). 24 new hybrids as dual VEGFR-2/HADC inhibitors were synthesized and evaluated in vitro studies. One of them [7-(4-(4-bromophenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide] exhibited the most potent inhibitory activity against HDAC and strong inhibitory effect against VEGFR-2 in human breast cancer cell line (**e**, Fig. **1**). These results demonstrate that this new hybrid compound is a potential agent for cancer therapy [88].

Estrogen signaling is mediated by intracellular estrogen receptors (ERα and ERβ), members of the nuclear receptor superfamily that regulate gene expression through binding to DNA response elements associated within target genes [89]. ERα is well characterized as a mediator of cell proliferation, especially in breast cancer cells in response to estrogen [90]. Cancer growth can be inhibited targeting ERS which are regulators of cell proliferation. As a key factor in breast cancer growth, ERα has been effectively targeted in breast cancer. Two classes of competitive ER inhibitors have been developed for breast cancer treatment. Tamoxifen and raloxifene, and pure antiestrogen are selective estrogen receptor modulators (SERMs) [91]. ICI-164,384 and fulvestrant act as selective estrogen receptor downregulators (SERDs [92]. Exo-5,6-bis-(4-hydroxyphenyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-sulfonic acid phenyl ester (OBHS) is a new bifunctional hybrid agent having improved efficacy and selectivity while retaining high affinity for ER was synthesized with the incorporation of SAHA into unique ER. The OBHS-HDACI is a hybrid formed via conjugation of SERM and HDACIs representing a novel and efficient estrogen receptor antagonists for breast cancer therapy [93]. SERD/HDACI synthesized from ICI-164,384 and fulvestrant is another novel dual-functional hybrid proposed as a potential therapeutic agent for breast cancer. These results support the synthesis and application of hybrid molecules with inhibitory activity against both HDAC's and estrogen receptor.

Inclusion of a zinc binding group into the side chain of ICI-164,384 resulted in gain of HDACI activity while keeping the antiestrogenic activity. Combination of HDACI's with anti-estrogens in breast cancer treatment may lead to the achievement of more efficient therapies. The aim of future studies should focus on improving affinity for each target and testing efficacy in preclinical [94].

3.4. Natural Product Hybrid Compounds

Recent studies have shown that molecular hybrids of biologically active natural molecules can be used as powerful therapeutic agents in many diseases including cancer [16]. Synthesis of natural product hybrids represents a promising approach in the development of more efficient treatment modalities in cancer. There is a continuous and increasing interest to use natural products in the chemotherapeutic drug discovery field because they are biologically available and have potent therapeutic effects. The efficiency of the new hybrid compounds synthesized combining the dietetic phytochemicals with the conventional synthetic drugs used in the treatment of cancer and the interactions within the dietetic phytochemicals are under heavy investigation currently.

Curcumin (diferuloylmethane) is natural and yellow colour spice isolated from *Curcuma longa.* It is a natural product present in turmeric and the majority of turmeric's therapeutic effects is due to curcumin [95]. Curcumin has been shown to be cytotoxic in vitro in many cancer cell lines and in vivo cancer models [25, 96-98]. The efficiency of curcumin in cancer studies has led it to be used in the synthesis of new hybrid compounds. But, curcumin is very poor in aqueous.

The flavonoids are naturally occurring important components of the human diet [99]. Their potential role in the prevention of human cancer has been under heavy research for decades. The following can be stated among the cancer chemopreventive effects of dietary flavonoids such as quercetin inhibiting potently the STAT3 signaling pathway [100], and genistein inhibiting specifically tyrosine kinase and topoisomerase II [101]. Chromone is serves as pharmacophore for genistein and quercetin, and other dietary natural products. It is a heterocyclic scaffold with anticancer effects [102, 103]. Ten asymmetrical new hybrid compounds of dietary curcumin and genistein have been designed and synthesized. These hybrid compounds were shown to be more potent than curcumin and genistein on inhibiting cell proliferation in human prostate cancer cells [104].

Multiple myeloma (MM) is an aggressive tumour having a destructive effect on bone marrow. MM promotes tumour growth and osteolysis through expression and secretion of growth factors, adhesion molecules, exosomes, miRNAs, chemokines and inhibitors [105]. Bone marrow angiogenesis plays an important role in the development of MM. Thalidomide has been investigated in MM [106]. Curcumin has been shown to have cytotoxic effects in MM and enhanced the effects of other therapeutic agents, including thalidomide, in experimental MM models [107]. Five hybrid compounds of thalidomide and curcumin have been synthesized as potential treatment agents for MM [108]. Two hybrids of thalidomide and curcumin, exhibited more potent cytotoxic effects in comparison to curcumin and thalidomide alone which might be attributed to the induction of ROS production and cell arrest at the S phase leading to significant apoptosis of MM cells lines (**f**, Fig. **1**). They also inhibited NFκB activity in human lung cancer cell line [108]. These studies demonstrated that the hybrid compounds of thalidomide and curcumin were more potent than the single agents while keeping the properties of both agents. All these results proved that the hybrid drug design could lead to novel treatment modalities in MM therapy.

Artemisinin is a natural product isolated from *Artemesia annua L*. It has anti-inflammatory effects and is used as an antimalarial drug [109]. It has been proposed to have anticancer activities [110]. The endoperoxide moiety is responsible for its anti-malarial and anti-cancer effects. Reduced heme or ferrous iron activates the endoperoxide bond leading to the formation of carbon-centered radicals which are cytotoxic alkylating agents [111, 112]. Recent studies have demonstrated the anti-cancer activity of artemisinin and its derivatives [113-117]. Different hybrid compounds of artemisinin and its derivatives with chemotherapy agents have been investigated in different cancers targeting multiple pathways [118, 119]. Indoloquinoline alkaloids are becoming popular due to their DNA intercalating properties [120]. Recent research have demonstrated that plant alkaloids are promising candidates for new drugs against several cancers [121]. Antiproliferative strengths of dihydroartemisinin-indoloquinoline hybrids were screened in a study [122]. Antiproliferative activities of new artesunate-indoloquinoline novel hybrid compounds prepared and characterized were evaluated in different cancer cell lines. These studies proved that the indoloquinoline skeleton improved the antiproliferative activity and selectivity of artemisinin towards cancer cell lines. There are further research studying the effects of hybrid compounds synthesized using different modifications of indoloquinoline and different artemisinin analogues.

Ageladine A, isolated from the sponge *Agelas nakamurai*, is a marine natural product [123]. Studies demonstrated that Ageladine A is an inhibitor of matrix metalloproteinases (MMPs) [124-126]. Several hybrids of Agelidine A with different anticancer agents were synthesized and tested in different human cancer cell lines [127]. Several hybrid agents of Agelidine A with semicarbazide/thiosemicarbazide derivatives have been investigated demonstrating marked anticancer activity [128]. Hybrid-based design, synthesize, and evaluate a series of Forty semicarbazide/thiosemicarbazide-Ageladine A hybrids were designed, synthesized, and evaluated for their cytotoxic effects using MTT assay technique in five human cancer cell lines. In addition to their enhanced cytotoxic activity, they showed also anti-invasive potential indicated by their inhibitory activity against MMP-2. These results propose them as promising novel anticancer drugs [129].

4. NEW STRATEGIES FOR HYBRID COMPOUNDS

Resistance to single or multiple chemotherapeutic drugs is a major obstacle and limitation in cancer therapy. Failure of chemotherapy may occur as a result of intrinsic or acquired drug resistance of the cancer cells to chemotherapeutic drugs which are called multidrug resistance (MDR). Overexpression of ATP-binding cassette (ABC) transporters

has been shown to be responsible for MDR. ATP-binding cassette (ABC) transporters are a family of transporter proteins that contribute to drug resistance via adenosine triphosphate (ATP)-dependent drug efflux pumps. The most typical efflux pump in the cell membrane is P-glycoprotein (P-gp) belonging to the ABC family of transporters. Inhibiting the function of ABC drug transporters by inhibitors or modulators ameliorate drug sensitivity in MDR cancer cells. ABC transporter inhibitors, also called MDR modulators, chemosensitizers, or MDR reversal agents, are able to reverse resistance against anticancer drugs [130].

The new hybrid compounds synthesized by combining the chemotherapeutic drug and modulator are thought to be more effective in overcoming the drug resistance and providing more efficient therapy. In a study, hybrid compounds synthesized from 5-FU and propafenone showed interactions with P-gp proposing it a potential drug as an MDR modulator (**g**, Fig. **1**) [131]. These hybrid compounds were evaluated measure of hydrophobicity and total polar surface area, which show their interaction with P-gp.

Egonol (EG) and homoegonol (HE) are a group of biologically active natural products containing benzofuran heterocycle [132]. The cytotoxic activities of EG and HE, were evaluated in different tumour cell lines [133]. A hybrid compound was synthesized from artemisinin and egonol and its cytotoxicity was compared with the cytotoxicity of the single agents in acute lymphoblastic leukemia (ALL) cells and multidrug-resistant (ALL/ ADR) human leukemia cells. The IC_{50} value of the hybrid compound was found higher than the IC_{50} values of single agents indicating its potency in overcoming the drug resistance and increasing the sensitivity of the cells to the hybrid compound [134].

Mammalian target of rapamycin, also defined as mTOR is a protein kinase functioning in the PI3K/AKT/mTOR signaling pathway. The mTOR plays important role in cellular functions such as survival, cell proliferation, and growth [135]. Dysregulation of m TOR on cell growth has been reported in cancer [136]. The mTOR pathway is activated in many cancers [137, 138]. Attempts to intervene the mTOR pathway are under heavy research. Rapamycin is a natural product inhibitor of mTOR. Although it has high specificity for mTOR, its efficiency is dose dependent [139]. Its long term use may cause adverse effects such as hyperlipidemia [140]. In vitro and in vivo recent studies demonstrated that rapamycin and its derivatives exert potent and wide anticancer actions [141-144].

Several studies have proved the key role of phosphoinositide 3-kinases (PI3Ks) enzymes in the development and progression of many cancers. Therefore, there is a big interest to develop and test PI3Ks inhibitors [145]. A hybrid compound synthesized from rapamycin and wortmannin was shown to be a potent covalent inhibitor of PI3Ks, inhibiting tumour growth in vivo xenograft model [146].

The current studies in this field searching for next generation drugs will lead to the discovery of several new hybrid natural products having efficient and potent activities in cancer therapy and to overcome drug resistance [147-149].

CONCLUSION

Although several conventional anticancer drugs have been discovered and are widely used in cancer therapy, most of them have adverse side-effects and they cannot distinguish selectively cancer cells from normal cells. There is an obvious need for the discovery of novel anticancer drugs. In order to achieve this goal, several hybrid potential anticancer agents such as gene expression modulators, signal transduction inhibitors, angiogenesis inhibitors, apoptosis inducers, and hormone therapies are under heavy research [148, 150]. These attempts will render attacking a highly important goal for the multiple targets via hybrid compounds.

LIST OF ABBREVIATIONS

5-FU	=	5- Fluorouracil
ABC	=	Adenosine Tri Phosphate Binding Cassette
CA4	=	Combretastatin-A4
c-Met	=	Cellular Met Protein
DCA	=	Dichloroacetate
DNA	=	Deoxyribo Nucleic Acid
E2F	=	E2 Factor
EG	=	Egonol
ERα	=	Estrogen Receptor Alpha
ERβ	=	Estrogen Receptor Beta
FDA	=	Food and Drug Administration
G0	=	Growth 1 Phase in Cell Cycle
G1	=	Growth 0 Phase in Cell Cycle
G_2/M	=	Growth 2 Phase/Mitosis Phase in Cell Cycle
GPx	=	Glutathione Peroxidase
GSH	=	Glutathione
GST	=	Glutathione S-transferase
HAT	=	Histone Acetyltransferase
HCC	=	Hepatocellular Carcinoma
HDAC	=	Histone Deacetylase
HDACI		Histone Deacetylase Inhibitor
HDLP	=	Histone Deacetylase-Like Protein
HE	=	Homoegonol
HGF	=	Hepatocyte Growth Factor
Hsp90	=	Heat Shock Protein 90
IC50	=	The Half Maximal Inhibitor Concentration
MDR	=	Multi Drug Resistance
miRNA	=	Micro Ribo Nucleic Acid
MM	=	Multiple Myeloma
MMP	=	Matrix Metalloproteinase
MR-4	=	3,4,4',5-tetramethoxy-trans-stilbene
mTOR	=	Mechanistic Target of Rapamycin

MTT	=	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
NFκB	=	Nuclear Factor Kappa B
NO	=	Nitric Oxide
OA	=	Oleanolic Acid
OBHS	=	Exo-5,6-bis-(4-hydroxyphenyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-sulfonic acid phenyl ester
OC		Ovarian Cancer
p53	=	Protein 53
P-gp	=	Permeability Glycoprotein
PI3K	=	Phosphoinositide 3-Kinase
PI3K/Akt	=	Phosphoinositide 3-Kinase/Protein Kinase B
PL	=	Piperlongumine
PMS	=	2,3',4,4',5'-pentamethoxy-trans-stilbene
Pt (II)]	=	Platinum (II)
PTT	=	Podophyllotoxin
QCA	=	Quinone Methide-Cinnamaldehyde
ROS	=	Reactive Oxygen Species
RSV	=	Resveratrol
RTK	=	Receptor Tyrosine Kinase
S	=	Synthesis Phase in Cell Cycle
SAHA	=	Suberoylanilide Hydroxamic Acid
SERD	=	Selective Estrogen Receptor Downregulator
SERM	=	Selective Estrogen Receptor Modulator
SOD	=	Superoxide Dismutase
STAT3	=	Signal Transducer and Activator of Transcription 3
TKI	=	Tyrosine Kinase İnhibitor
TMS	=	2,3',4,5'-tetramethoxy-trans-stilbene
UV	=	Ultra Violet
VEGF	=	Vascular Endothelial Growth Factor
WHO	=	World Health Organization

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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