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A Mini Review on Triazine Derivatives as Anti-Cancer Drugs

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Abstract: *Though several drugs have been found to be effective in combating cancer to some extent yet, no such drugs have are yet commercially available for treating cancer. Hence the search for effective pharmaceutical formulation against the neoplastic cells continues. Triazines being highly versatile and having a stable structural configuration are a wonderful and popular choice for developing drugs against cancer. Because of their unique heterocyclic scaffold, ease of substitution and broad spectrum bioactive potentials, the triazine compounds are of interest for developing anti-cancer drugs. The electron-deficient 1,3,5-triazine core allows extensive modification of the chemical configuration. This helps to make potent triazine derivatives with enhanced efficacy, improved selectivity, increased potency and suitable pharmacokinetic properties. Studies reveal a good number of triazine-based molecules with potent and significant anticancer activity against a wide range of malignancies. Such triazine derivatives have been reported to be effective against lung, breast, colorectal, prostate and hematological cancers. This mini review summarizes recent advances in the design, structure–activity relationships and molecular mechanisms of triazine derivatives as anticancer agents, highlighting their therapeutic potential and future prospects in anticancer drug development.*

Keywords: Triazine, Anticancer, Triazine derivative, Cytotoxic

I. INTRODUCTION

Cancer is the most common public health problem worldwide and it is one of the leading causes of death throughout the world. The main treatments involve surgery, chemotherapy, and/or radiotherapy. Chemotherapy involves the use of cytotoxic agents to destroy tumour cells. It causes bone marrow suppression, gastrointestinal tract lesions, hair loss, nausea and the development of clinical resistance because cytotoxic agents act on both tumour cells and healthy cells. Cytotoxic agents can be replaced by extremely powerful alkylating agents and antimetabolites. Since the early success of these treatments, a large number of additional anticancer drugs have been synthesized, modified and developed in the last few decades [1,2].

In this regard, triazines scaffold have attracted attention due to their remarkable activity against a wide range of cancer cells. Triazine can also relate to numerous beneficial targets and their analogues have auspicious *in-vitro* and *in-vivo* anti-tumour activity. Fused molecules can improve efficacy and drug resistance and diminish side effects, and numerous hybrid molecules are beneath diverse stages of clinical trials, so hybrid derivatives of triazine may offer valuable therapeutic involvement for the dealing of tumours [3].

Triazines are an important class of six-membered aromatic heterocyclic compounds in which three carbons replaced by nitrogen. It exists in several isomers (1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine) and they are distinguished from each other by the positions of their nitrogen atoms. Among them, 1,3,5-triazine, also called s-triazine, has three easily modified sites at positions 2, 4, and 6 usually used for modulating its physicochemical and biological activities. Therefore, various kinds of s-triazine derivatives as well as their hybrid derivatives of have been isolated due to their

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remarkable activity against a wide range of cancer cells. This mini review focuses on the anticancer activities of triazine based compounds and their structure activity relationships (SAR) and mechanistic insight [4].

II. TRIAZINE DERIVATIVES AS ANTI-CANCER AGENTS

Reason of use of triazines: Triazine has a hexagonal ring containing carbon, hydrogen and nitrogen that enable them to bind with many target molecule and this nature is very useful for oncology [5]. The isomeric form of triazine is frequently used as core scaffold of fused ring such as triazolotriazines that mimic the purine base of DNA [6,7]. The triazine scaffold has high modularity and reactivity. It is a highly soluble compound so body can easily absorb it. Triazine can only target the cancer tissue rather healthy tissue which reduces the toxicity. It can easily overcome the resistance given by cancer cell because cancer cell could have recognize and pump out the drug [8]. Some examples of potent triazine derivatives with anti-cancer activity are represented in brief in Table 1.

Table 1. Triazine Derivatives as Anti-cancer Agents, their mechanism of actions and Physiological interactions

Sl.	Triazine derivative	Structural features	Cancer type(s) studied	Mechanism(s) of anticancer action	Physiological interactions
1.	Chlorotriazines	1,3,5-Triazine core that have amino and chloro-substitutions	Lung, breast, colon cancer	Inhibition of cellular proliferation; induction of apoptosis	Show moderate-to-high cytotoxicity
	Amino-substituted triazines	Multiple amino or alkylamino groups on core triazine ring	Leukemia, prostate cancer etc.	Nucleic acid synthesis inhibition; cell-cycle arrest	Improved cellular uptake
2.	Triazine–quinazoline hybrids	Triazine core containing quinazoline moiety	Breast cancer	EGFR tyrosine kinase inhibition	Potent growth inhibition in EGFR-positive tumour cells
3.	Triazine–chalcone conjugates	Triazine scaffold remain coupled with chalcone	Breast cancer and cervical cancer	Microtubule disruption; Induction of apoptosis	Improved cytotoxic potency due to Hybridization
4.	Triazine–benzimidazole hybrids	Benzimidazole fused or connected to triazine ring	Lung, colorectal cancer	DNA binding; Induces ROS-mediated apoptosis	Broad-spectrum anticancer activity
5.	Folate-targeted triazines	Triazine conjugated with folic acid or analogs	Ovarian cancer, breast cancer	Folate receptor-mediated targeting	Improved selectivity towards cancer cells
6.	Triazine-based CDK inhibitors	Substituted triazines with heteroaryl groups	Breast cancer, melanoma	Cyclin-dependent kinase inhibition	Induce G1/S cell-cycle arrest
7.	Triazine–metal complexes	Triazine ligands linked with metal ions	Cervical cancer, liver cancer	DNA damage; mitochondrial dysfunction	Enhanced cytotoxicity compared to free ligands

Structure-Activity Relationships (SARs) of Triazine based anticancer compounds

It is well established that anti-cancer activity of s-triazine triazine core can be enhanced by introducing various substitutions in this core. Structure-Activity Relationship (SAR) studies show that s-triazines contained electron-withdrawing groups such as 4-chloro- and 4-amino on the benzene ring of the phenylamino-s-triazine scaffold increases its selectivity and limit toxicity against normal cells. In addition, the morpholino and benzimidazole groups were also a common substituent present in the structure of lead compounds for strong anticancer activity. Furthermore, various hybrids, conjugates and metal complexes of s-triazine scaffold may enhance the anticancer activity. The overview of functional aspects of triazine and its main derivatives that are used in anti-cancer activity are given in Fig. 1.

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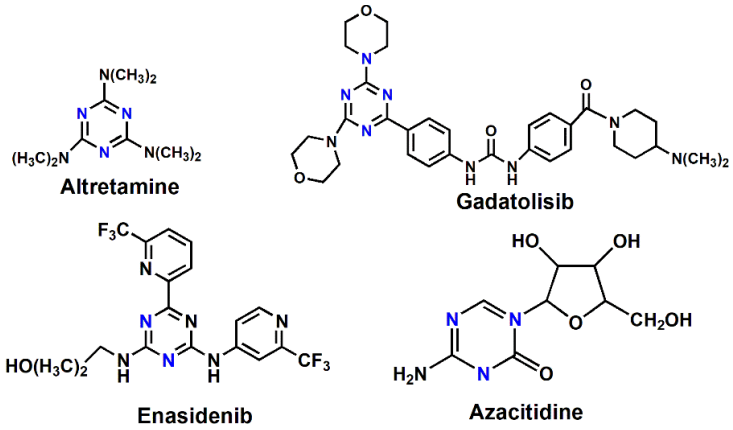

Fig.1. Various Triazine derived compounds as anti-cancer agents

Chloro- and amino triazine derivative containing chloro- and alkyl amino- groups attached with the carbon atoms of triazine could be a promising lead compounds for developing new target-selected anticancer compounds. Hybrid triazine-quinazoline derivatives are derived by substituting the s-triazine ring with morpholine or aniline groups. These are potent anticancer agents that enhance EGFR inhibition. Similarly, triazine-chalcone conjugates represent a promising class of synthetic anticancer agents designed by combining the s-triazine and chalcone, showing potent antiproliferative activity against various cancer cell lines. The combination of a benzimidazole core with s-triazine and various amines (primary/secondary) enhances cytotoxic effects of trizine-benzimidazole hybrids. Folate-targeted triazines destroy cancer cells by combining the receptor ability of folic acid with the cytotoxic action of triazine-based compounds. Triazine-based metal complexes have been isolated by using Cu(II), Pt(II), or Pd(II) with s-triazine derivatives. These metals enhance the biological activity of triazine based ligands [9,10].

Mechanisms of Action of Triazine-based anticancer compounds

The derivatives of triazine do not attack the cancer cell directly rather it targets specific molecules which are responsible for cancer development. Some triazines are antifolates because it inhibited the activity of dihydrofolate reductase which is the key enzyme that synthesize thymidine required for DNA replication. Some triazines the enzyme protein kinase that helps the cancer cell to proliferate uncontrollably. Many triazine derivatives triggers apoptosis in Cancer cell. Some triazines prevent tubulin protein assembling that is necessary for cell division [11]. The triazine derived anticancer compounds have been reported to work through various mechanisms including inhibition of certain enzymes and signaling molecules involved in the pathogenesis of cancer. They also act by disrupting the replication, repair and transcription of DNA in neoplastic cells. Others have been reported to act *via* induction of apoptosis, arresting cell cycle. Triazine derivatives have also been found to exhibit their anticancer efficacy by inhibiting the various cytokines and signalling molecules involved in induction of oxidative stress and inflammation [12,13].

Inhibition of kinases or other enzymes

It has been reported that triazine compounds induce cell cycle arrest, commonly at the G_1 or G_2/M phase. This effect is intermediated *via* down-regulation of cyclins and cyclin-dependent kinases (CDKs) and up-regulation of CDK inhibitors such as p21 and p27. Cell cycle arrest prevents mitotic progression and sensitizes cancer cells to apoptosis. Some specific triazine derivatives inhibit dihydrofolate reductase (DHFR) and related folate-dependent enzymes. DHFR inhibition leads to depletion of tetrahydrofolate, an essential cofactor for purine and thymidylate synthesis. As a result, DNA and RNA synthesis are hindered, leading to cytostatic or cytotoxic effects in tumor cells [14].

DNA intercalation or damage

Several triazine derivatives function as antimetabolites, interfering with DNA replication and transcription. By mimicking endogenous nucleotides or inhibiting enzymes involved in nucleotide biosynthesis, these compounds block

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DNA synthesis, leading to reduced cell proliferation. Rapidly dividing cancer cells are chiefly susceptible to this mechanism [15].

Challenges in developing triazine derivatives as anti-cancer drugs

Designing triazine-based anticancer drugs comes with several challenges. These include 'selectivity issues' i e. the compounds may not be able to distinguish between normal cells and neoplastic cells and hence may not precisely only target cancer cells. Damaging normal cells may lead to toxicity and serious side effects. Additionally, like in case of any other drugs, cancer cells can develop resistance to triazine-based drugs due to long term use thereby reducing their effectiveness. It is important to understand in details the optimizing pharmacokinetics of the triazine-based anticancer drugs. It is also essential to focus on improving solubility and understanding exact precise mechanism of action of the drug molecules in order to overcome the associated challenges. Furthermore, cytotoxicity induced by long term use of such triazine-based anticancer drugs in certain tissues or organs can limit the therapeutic window of these compounds.There also remains a possibility of drug drug interactions with these triazine based anticancer drugs [16,17]. Addressing these challenges needs elaborate research, clinical trials, interdisciplinary research and strategic molecular designing and development of the triazine-based compounds in order to get effective and safe triazine-based anticancer drugs (Fig 2).

Future directions for research and development

Future research prospects with triazine-based anticancer drugs are bright and promising. Current studies are primarily focused on optimizing the efficacy and safety profiles of such triazine-based anticancer formulations. One of the main focus of investigation is the designing of novel and safe triazine derivatives with improved selectivity and efficacy against specific target cancer cell lines. Combination therapies and synergistic therapies are also being investigated by researchers all around the globe. Triazine-based drugs with anticancer potentials are being paired with existing chemotherapeutic agents leading to enhanced anticancer efficacy. On the other hand, triazine-based compounds are being paired with antioxidant drugs derived from nature that mitigate the cytotoxicity of the triazine based drugs by removing the Reactive Oxygen Species (ROS) from the system [17,18]. Advances in medicinal chemistry and fields if pharmacology powered by modern technologies like computational biology, artificial intelligence and machine learning are making it possible to develop triazine-based compounds with improved pharmacokinetic properties i.e increased bioavailability, reduced cytotoxicity and minimized side effects. Furthermore, the identification of specific molecular targets and biomarkers is expected to facilitate the development of personalized anticancer medicinal approaches utilizing triazine-based anticancer drugs [19,20]. Overall, the continued exploration of triazine-based compounds shows a bright path ahead for the discovery of new and effective treatments for combating various types of cancer with minimum side effects (Fig. 2).

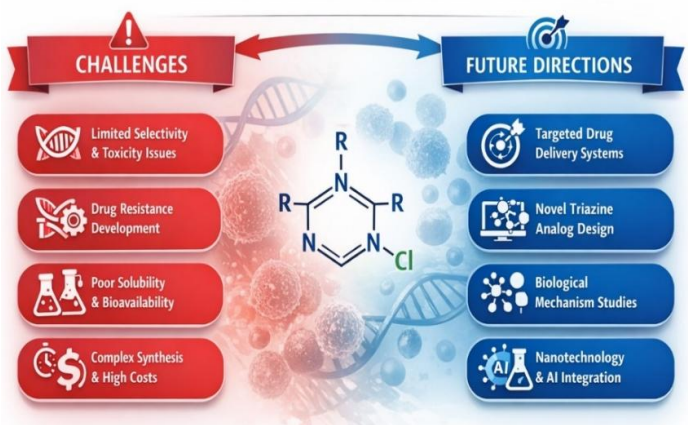

Fig. 2. Challenges and Future Directions in Triazine-based Anticancer Drug Development

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III. CONCLUSION

1,3,5-triazine scaffold are a class of compounds that are highly significant in anticancer drug discovery. Their wide structural versatility, the aromatic core that is deficient in electron, ease of functional substitution and modification at several positions help to develop diverse derivatives with increased anticancer activity and improved pharmacokinetic properties. Recent *in vivo* and *in vitro* studies reveal that triazine-based compounds exhibit significant anticancer activity against different types of malignancies, including prostrate, colorectal, breast, lung, hematological, and ovarian cancers. The anticancer potency of triazine derivatives is facilitated through multiple mechanisms that includes inhibition of certain enzymes associated with progression of cancer, disruption of DNA synthesis and repair, induction of cell cycle arrest, generation of ROS, and activation of apoptosis pathways. Designing strategies involving structure–activity relationships, adapting targeted delivery strategies like modern studies for optimization of drug efficacy and dose in large scale followed by experimental validation, comprehensive preclinical and clinical evaluation are necessary to maximally utilize the anti-cancer efficacy of the triazine based drugs in order to combat certain types of cancer and save human lives. To conclude, triazine derivatives constitute a vast, valuable and versatile scaffold for anticancer drug development. Detailed investigation into their molecular mechanisms and therapeutic optimization may help significantly for safer and more effective utilization of these anticancer agents.

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