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REVIEW ARTICLE

Chalcone Scaffolds as Anticancer Drugs: A Review on Molecular Insight in Action of Mechanisms and Anticancer Properties

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Abstract: Cancer is the deadliest disease worldwide and the development of safer chemical entities to treat cancer is one of the major challenges of medicinal chemistry. The emergence of new cases every year and the development of multiple drug resistance against available molecular entities have turned the focus of researchers towards natural products. Chalcones are pharmacologically active compounds, present in plants, which have been derivatized and screened by many researchers for the treatment of cancer. Chalcones, consist of 1,3-diaryl-2-propen-1-one, is one such class exhibiting broad anticancer activities against various cancerous cell lines.

The objective of this review article is to analyze the antitumor activity of the reported chalcones *via* distinct mechanisms adopted by these molecules underlying their inhibitory activity. The primary focus of this review is to bring the attention of researchers towards the latest and important chalcones and their derivatives having potent anticancer activity adding their possible action of mechanisms against cancerous cell lines The recent literature was surveyed and it was found that chalcone analogs with electron donating groups, indolyl, quinolone, pyrazol-ol, hydroxyaminobenzamide, hydroxamic acid and pyridyl- indole groups have shown promise as potential anticancer agents following various mechanisms. Most chalcones were found to induce significant cell cycle arrest at G_2/M phase hence leading to apoptosis. A number of synthetic chalcones exhibited higher efficacy due to their ability of potent tubulin polymerization as well as dynamic enzyme inhibitory activity. This review is an immense compilation of research regarding the mechanism of action of chalcones and their identification as a promising anticancer agent for future drug developments. Thus, this review article would pave the way and provide ample opportunities to design future generations of novel, highly efficacious anticancer molecules with minimal toxicity.

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1. INTRODUCTION

Chalcones are pharmacologically active compounds that form the central core of a variety of important biological molecules. These are the known precursors of flavonoids and are biologically synthesized by a variety of plant genera such as Sophora, Glycyrrhiza, Scutellaria, Dorstenia, Parartocarpus, Ficus, and Artocarpus [1]. In the community of researchers, chalcones are the molecules of interest not only because of their synthetic and biosynthetic pathway but also due to their broad spectrum of biological activities [2]. Cancer, the most lethal multifactorial disease after cardiovascular diseases, occurs due to uncontrolled, uncoordinated, and unwanted division of cells. The metastatic property of cancerous cells and its property to impair the process of contact inhibition in normal cells give it an incurable nature. Mutation in specific proto-oncogenes results in the formation of variant oncogenes that induce cancer. Several modern treatments like chemotherapy, immunotherapy, radiotherapy, and surgery are widely used but the intrinsic and acquired resistance of cancerous cells against anticancer drugs has proved to be a limitation for their potency against various cancer cell lines. Also, such treatments result in various side effects like CINV (Chemotherapy Induced Nausea and Vomiting), MDR (Multi Drug Resistant), pain, fatigue, appetite loss, *etc*. [3]. Therefore, the researchers are now focusing on botano-chemicals like chalcones, which are now being demonstrated as effective cytotoxic agents in various tumor cell lines [4].

1.1. Chemistry of Chalcone Scaffolds

These compounds bear a common 1,3-diphenylprop-2-en-1-one framework with its two rings linked through a ketovinyl chain, together known as a chalconoid (Fig. **1**). Chalcones have a three carbon α,β-unsaturated carbonyl system with delocalization of electrons on both the rings. This α,β-unsaturated carbonyl or a keto ethylenic group is very reactive towards various binucleophilic reagents, which produce a wide library of heterocyclic chalcone derivatives like indolyls, pyrazol-ol, phenylpyrazoline and isoxazole, quinolone, hydroxamic acid derivatives and many more. These chalcone scaffolds can be synthesized *in vitro* by Claisen-Schmidt condensation or Aldol condensation of aryl methyl ketones with aryl aldehydes. In the present day drug discovery studies, there is an upsurge in the scientific articles reporting the amalgamation of various naturally occurring or synthetic chalcones with pharmacophores of known therapeutic potential [2]. The activity profiles of these hybrids are studied broadly which clearly establishes the importance of the molecule under study. Various researches have proved the pharmacological potential of chalcones, depending on their substituents, as effective antimicrobial, antiviral, antibacterial, antifungal, antimalarial, antileishmanial, antinociceptive, anti-inflammatory, analgesic, antiplatelet, antioxidant, anti-ulcerative, anticancer, immunomodulatory compounds [5-13]. They also act as inhibitors of varied chemical mediators and enzymes including tyrosinase, oxidoreductase, esterase, leukotriene B4, aldose reductase and so forth [14].

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