Review Paper:

Harnessing of Chalcones in Cancer Therapy

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Abstract

Cancer is a leading global health concern, causing millions of deaths annually. It results from uncontrolled cell proliferation, often driven by genetic mutations. Chalcones, a subclass of flavonoids, have emerged as potential anticancer agents due to their modifiable chemical structure and diverse biological activities. Studies have demonstrated their effectiveness against various cancer cell-lines including MCF-7 and Caco-2, with certain derivatives acting as potent enzyme inhibitors. Given their promising anti-proliferative properties, chalcones hold significant potential for the development of novel anticancer drugs and overcoming drug resistance. This review is needed to consolidate recent advancements, to explore novel chalcone derivatives and to assess their clinical relevance, providing a deeper understanding of their role in cancer treatment and potential health risks. This study explores chalcones potential as anticancer targets, highlighting their molecular mechanisms. It examines natural sources of chalcones, focusing on key compounds like butein, curcumin and xanthohumol with significant anticancer properties.

The review also covers synthetic chalcones and chalcone hybrids, emphasizing structure modifications for enhanced efficacy. Furthermore, it evaluates their role in overcoming drug resistance and bioavailability challenges, offering a comprehensive perspective. Given the rising interest in natural and synthetic bioactive compounds, this review is essential for guiding future research and drug development. By consolidating diverse findings, it provides a critical update on chalcones' therapeutic potential, aiding in the discovery of more effective anticancer treatments.

Keywords: Chalcones, Caner Therapy, Chalcone Hybrids, Natural Sources, Molecular genetics.

Introduction

Cancer arises from the unchecked proliferation of cells and causes many of fatalities globally every year. Its origin and evolution are highly variable. A diversity of approaches such as surgery, chemotherapy and radiation, is in cancer treatments, either unaided or in grouping[21]. Conversely, multidrug resistance (MDR) and secondary complications remain main barriers to the operative treatment of cancer. It encompasses approximately 270-281 distinct types of disorders[1]. Researchers have outlined various stages of cancer, emphasizing numerous genetic alterations involved in its development. These mutations lead to abnormal cell growth. Hereditary genetic defects play a pivotal role in cell proliferation.

Advances in molecular techniques and bioinformatics have provided valuable insights for early detection and optimal treatment strategies. Recent molecular genetic studies have shed light on the cancer pathways. Nutrition rich fruits, tubers, spices, grains and legumes are related with a minor occurrence of cancer and further prolonged diseases; however, the precise mechanism by which these dietary elements and their bioactive compounds alleviate these conditions, is to be understood. Chalcones, members of the polyphenolic compound family and byproducts in flavonoid biosynthesis, have structural diversity and may interact with multiple pharmacological targets.

Due to their potential for both synthetic and biosynthetic production, as well as their wide ranging organic happenings including antioxidant, anti-inflammatory, antidiabetic, chemo-preventive and anti-cancer effects, chalcones have attracted considerable attention. Chalcones, which would be appropriate to the flavonoid class and function as byproducts in flavonoid bio-synthesis, show structural diversity and possess the potential to interact with various pharmacological targets. Members of the chalcone family have attracted considerable scientific interest owing to their capacity for both synthetic and biosynthetic production, alongside their extensive spectrum of biological events, containing anticancer, anti-inflammatory, antidiabetic, chemopreventive and antioxidant effects[39].

Chalcone compounds possess the chemical structure of 1,3-diaryl-2-propen-1-one, a configuration that is easily modifiable to alter the biological possessions of these molecules[41]. Chalcones exhibit an extensive variety of biological actions owed to the presence of diverse functional groups, which enhance their ability to bind numerous molecular targets and interact with other chemicals. As such,

chalcones are regarded as promising frameworks for the expansion of unusual anticancer drugs. Furthermore, the conjugation of the chalcone structure with alternative anticancer pharmacophores leads to fusions capable of overcoming drug opposition and improving therapeutic specificity, thereby offering a favorable approach for the creation of new anticancer therapies.

Chalcones are flavonoids resulting from plants, categorized under the flavonoid family and are known for their diverse regulatory and cytoprotective effects. They possess antibacterial, antifungal, anti-inflammatory, antioxidant, anticancer and antidiabetic activities. Immunoblot analysis revealed that chalcones reduced the appearance of Cdc-2, cyclin-A, cyclin-B1and proteins, while simultaneously increasing the intensities of p-21 and p-27. The chalcone molecule's structure comprises of two aromatic rings associated by a three-carbon aliphatic chain. The α, β-rings of chalcone are merged by a highly electrophilic, α, β-unconstrained carbonyl system, which adopts a linear or non-linear[4] form. This system resonates π-electron network spanning both aromatic rings.

Chalcones represent an excellent source for the development of numerous novel heterocycles with favorable pharmacological profiles and substantial therapeutic potential. These compounds are recognized for their involvement in various biological processes, making them highly intriguing. Organizational amendments to the chalcone rings have managed to considerable variation, proving beneficial for the design of fresh therapeutic agents.

As a result, chalcones attracted ongoing attention in both academic and industrial research. The scheme, fusion and anti-tumor efficacy of chalcones were investigated in a concentration-dependent manner beside human breast adenocarcinoma MCF-7 cells[3]. Chalcones induced significant alterations in bio-chemical and molecular bounds, cell morphology and exhibited characteristics of apoptosis inducers, positioning them as promising candidates for cancer therapy, particularly in overcoming drug resistance. Bischalcone products were evaluated for their capability to constrain development in MCF-7 and Caco-2 human cancer cell lines, as well as for their activity against xanthine oxidase *in vitro*.

The bischalcone with a fluoro group at the 2nd or 5th position of the B-ring demonstrated strong enzyme inhibition, with IC-50 values in the low micromolar range. Novel Pt-(IV) complexes of chalcone analogs were produced and assessed for their anti-proliferative effects expending the MTT assay.

Chalcones were further investigated for their anti-proliferative happenings in a range of human cancer cell lines including cervical (HeLa), ovarian (Caov-3), TRAIL-resistant breast (MCF-7, MDA-MB-231), T-lymphoblastoid (CEM-SS), lung (A549), liver (HepG2), colorectal (HT-29), nasopharyngeal (CNE-1) and erythromyeloblastoid (K-562) cell lines[35].

Chalcones potential for anticancer target

Chalcone composites exhibit a compound structure of 1,3-diaryl-2-propen-1-one, existing as either trans(E)-4 or cis(Z)-5 isomers, characterized by two aromatic rings connected by a 3 carbon incomplete saturation carbonyl framework[2]. These compounds possess multiple substitutable hydrogen atoms, facilitating various synthetic strategies for the creation of chalcone derivatives. A key feature of these synthetic approaches is the strengthening of two aromatic classifications, incorporating nucleophiles and electrophiles clusters, to form the chalcone scaffolds[13].

The synthesis of the standard chalcone scaffold (1,3-diphenyl 2-propen 1-one) employs several retort methods including Claisen Schmidt compression, carbonylative Heck coupling solid acid catalyst mediated reactions. The significant cancer-inhibitory potential of naturally found chalcones can be attributed to three primary strategies for synthesizing anticancer chalcones: Structural modifications to the aryl rings, replacement of the aryl rings to form hetero-aryl frameworks and molecular bond formation done electron delocalization with additional pharmacologically relevant scaffolds to increase their anticancer possessions[5]. Chalcones are integral intermediates in flavonoid biosynthesis and are commonly found in various natural products.

These compounds exhibit a wide spectrum of organic events, likely unpaid to their compact structure properties, that allowed to interact with a range of biological molecules and to facilitate their reactive binding with specific targets. The molecular framework of chalcones can be easily adapted to modify their complete biological action. Chalcones have demonstrated the ability to target multiple biological molecules in diverse screening assays including MDM-2/p-53, αβ-tubulin, NF/κB, ABCG-2/P-gp-BCRP, VEGF, VEGFR/2 kinase and MMP-2/9[19]. The broad spectrum of bioactivity exhibited by chalcones suggests a possibly promiscuous directing outline, which grants challenges for their clinical expansion. Recently, Vutey and co-authors[38] identified a hepatotoxicity linked to flavokawain-A.

The compounds found in kava contribute significantly to hepatotoxicity through mechanisms such as glutathione depletion, cytochrome P450 (CYP) inhibition, the formation of reactive metabolites, mitochondrial toxicity, and/or cyclooxygenase activity. A transformation in the p-53 gene primes to the production of an abnormal enzyme that severely disrupts the molecular functions associated with p-53. This disruption of molecular and biological processes ultimately facilitates the development of cancer cells, establishing a critical link among the p-53 gene and cancer, with abnormalities in p53 detected in approximately 70% of cancer circumstances. Under usual circumstances, p-53 plays a pivotal character in regulating cell division,

apoptosis, senescence, angiogenesis, differentiation and DNA metabolism[37].

Moreover, several mutations within the p-53 gene originate in the DNA-binding domain and p-53 regulates gene expression during DNA imitation. The collaboration between p-53 and CDK/1-P2, CD-C2, is crucial in sustaining cancer cells through the G1 and G2 phases of the cell cycle. The inhibition of cathepsin H relative to cathepsin B suggests that the active site of cathepsin B is more susceptible to these compounds than that of cathepsin H, with these findings being consistent and logically supported by *in silico* docking studies[16].

Natural sources for chalcones

Chalcones form the foundational structure for a variety of naturally occurring bioactive complexes and have stayed broadly for several years. The chalcone family exhibits considerable operational variability and is able to broadly categorize into two primary types: classical chalcones and hybrid chalcones, both of which retain the core 1,3 diary-l/2-propen-1- one backbone[24]. These compounds are ubiquitously present in different plant organs such as seeds, roots, flowers, heartwood, leaves, rhizomes and buds, in species from genera like *Dorstenia, Sophora, Humulus, Parartocarpus, Scutellaria, Ficus, Morus, Artocarpus, Glycyrrhiza, Angelica*.

Notable anticancer chalcones sourced from nature include isoliquiritigenin, butein and isobavachalcone whose cancer-fighting potential has been extensively explored. ISL (2,4,4-trihydroxychalcone) is a prominent bioactive compound with a chalcone configuration, inaccessible since glycyrrhiza. ISL is recognized for its beneficial effectiveness in managing numerous malignancies such as melanoma, leukemia, lung, gastrointestinal, ovarian cancers, colon and breast. ISL has established the capability to suppress cancer cell relocation and incursion by inhibiting cell pro-liferation.

Butein, a bioactive flavonoid removed from the outer cortical layer of *Rhus verniciflu Stokes*, demonstrates considerable antitumor activity across multiple cancer types[28]. Butein exhibits anticarcinogenic effects in expanded cell lung cancer by inducing endo-plasmic reticulum stress-mediated generation of ROS and activating apoptotic paths, both *in vivo* and *in vitro*. Moreover, butein enhances G2/M stage capture and induces cell death by cumulative phosphorylation of ataxia telangiectasia and frontier kinases Chk-1 and Chk-2, resulting in the downregulation of cell separation cycle 25-C levels in HCC.

Isobavachalcone (IBC), a valued bioactive compound originates in plant life of the *Fabaceae* and *Moraceae* families, also demonstrates significant antitumor activity against various malignancies[29]. IBC exerts anti-pro-liferative and pro-apoptotic properties in HCC by directing the ERKs/RSK2 signaling path. Furthermore, IBC induces ROS-mediated apoptosis through the inhibition of thioredoxin reductase 1 (Trx-R1) in prostatic adenocarcinoma. In CRC cells, IBC constrains cell proliferation and brings apoptosis by disrupting the β-catenin signaling pathway/ AKT / glycogen synthase kinase 3.

Curcumin (CUR), a bischalcone imitative, is a naturally occurring composite extracted from *Curcuma longa*, a blossoming plant indigenous to South Asia, recognized for its corms, which remain processed to develop the seasoning turmeric[31]. CUR has been demonstrated to significantly inhibit the multiplying of HCT-15 cells and induce physiological cell death in a dose and time reliant manner. The morphological and organic characteristics of apoptosis along with the group of ROS were assessed in cells preserved with 30 and 50 µM of CUR. CUR treatment triggered the activation of caspase-3 and caused a time-dependent decrease in p-53 mRNA countenance and pre-mRNA treating factor-4B.

Xanthohumol (XH), a naturally arising prenylated chalcone primarily derived from the hop plant (*Humulus lupulus*), is well known for broad spectrum of genetic activities[6]. XH has shown significant anti-tumor effects in CRC by downregulating the manifestation of hexokinase-2 and inhibiting glycolysis. Furthermore, XH effectively suppressed the proliferation of CRC cells in both *in vitro* and *in vivo* models

Sappanchalcone (SPC) is a organic occurring chalcone composite secluded from the heart-wood of the *Sappan* tree (*Caesalpinia sappan*)[17]. This phytochemical has gained considerable attention in cancer investigation owing to its cytotoxic possessions against numerous cancer cell lines, particularly those associated with colorectal cancer. Investigations have examined the cytotoxic possessions of SPC on colorectal cancer cells, specifically the HCT-116 and SW-480 cell lines, which differ in their p-53 status. SPC interrupts mitochondrial membrane probable, regulates Bcl-2 family proteins and promotes the generation of ROS, ultimately triggering physiological cell death. In HCT-116 cells, SPC activates p-53, indicating a p-53 dependent apoptotic pathway. However, this effect is not observed in SW-480 cells which show no significant alterations in cleaved caspase expression, likely due to the lack of functional p-53[32].

Isoliquiritigenin (ISL) is a naturally occurring composite with a core chalcone configuration, categorized within the polyphenolic compound class. Renowned for its diverse probable health assistances, ISL is primarily sourced from the roots of licorice (*Glycyrrhiza glabra*) as well as several other plant species. Numerous *in vitro* investigations examined its anticancer properties, suggesting that ISL may constrain the proliferation of malignance cells and persuade physiological cell death, thereby emerging as a notable focus in cancer research. ISL has been demonstrated to induce G2 cell cycle arrest and modulate the methylation of the death

connected protein kinase-1 organizer in colon cancer cell lines, underscoring its character in manipulating the chromatin-level regulation of cancer-related genes[7].

Flavokawain-B (FK-B) is a certainly befalling composite isolated from the roots of *Alpinia pricei*, a herbal indigenous to precise areas, counting Taiwan[27]. This chalcone molecule, a member of the polyphenolic compounds family, is recognized for its bio-active possessions and its possible as an anti-cancer representative. It is present in the rhizome extracts of this plant which takes garnered significant consideration for its therapeutic possessions, predominantly its capacity to constrain cancer cell proliferation and activate numerous cellular pathways relevant to cancer behavior. FK-B has been exposed to markedly constrain the proliferation of HCT-116 colon cancer cells (CCCs) by persuading G2/M cell cycle detention and cell death. Furthermore, FK-B induces apoptosis through the elevation of intra-cellular ROS, activation of p-38 MAPK and up-regulation of GADD-153 expression[34].

Flavokawain-C (FK-C) is a bio-active composite with a distinctive natural source. This composite is mainly sourced from the kava plant (*Piper methysticum*), which is inherent to the South Pacific region. Significant cytotoxicity was observed in HCT-116 cancer cells, while normal colon cells exhibited limited sensitivity[30]. This study also investigated an organizationally associated composite, gymno-grammene (GMM), for comparative analysis, enlightening that FKC demonstrated considerable cytotoxic effects against HCT-116 cells whereas GMM displayed no such activity.

Derricin (DCN) and derricidin (DCD) are polyphenolic compounds of chalcone sub-class, naturally occurring phytochemicals with structurally similar chemical compositions[36]. These compounds have been explored for their possible therapeutic effects, predominantly in the realm of cancer research. Both DCN and DCD established important antiproliferative movement beside CRC cell lines, comprising of HCT-116 and DLD 1, by constraining cell evolution and modulating the cell cycle. Prominently, these properties remained predominantly observed in CRC cells, signifying a degree of discrimination.

This study further investigated the underlying mechanisms of these effects, revealing that the polyphenolic compounds modulated the Wnt/β-catenin signaling path, which is frequently implicated in CRC development. These results underscore the possibility of DCN and DCD as influencers of the Wnt pathway, prompting further exploration into their communications with detailed apparatuses of this pathway and their construction action relationships, thus necessitating additional research[9].

Licochalcone-A (LC-A) is a bio-active composite naturally occurring in several plant species, predominantly in the roots of licorice (*Glycyrrhiza*) species. *Glycyrrhiza uralensis* Fisch, normally known as licorice, serves as a chief foundation of LC-A[38]. This composite has attracted significant interest for its probable therapeutic belongings and has been investigated in several domains, with cancer treatment and anti-inflammatory applications. Research has focused on examining the properties of LC-A on detailed proteins and cellular processes. Both *in vitro* studies and *in vivo* experiments using a xenograft mouse model demonstrated that LC-A notably inhibited the expression of PD-L1, a critical immune checkpoint protein that is frequently upregulated in numerous human tumor cells.

Additionally, LC-A was shown to suppress the NF-κB signaling pathway, which shows an essential character in cancer cell existence, inflammation and immune responses, as well as modulating the Ras-Raf-MEK signaling pathway[8]. Garcinol (GAR), an imitative of chalcone, is a naturally occurring compound recognized for its anti-inflammatory and anticancer activities. Recent investigations have focused on its impact on cell proliferation in CCCs and exalted intestinal cell lines[14].

Isobavachalcone (IBC) is a bio-active compound extracted from *Psoralea corylifolia*, a prominent plant in traditional Chinese medicine. IBC attracted the researchers owing to its probable anticancer possessions and its capacity to restrain several cellular pathways implicated in cancer evolution[23]. IBC exhibited significant cytotoxic effects against CRC cell lines, containing SW-480 and HCT-116, in a dose and interval reliant method. Notable morphological alterations and a reduction in cell feasibility were detected in IBC treated cells, reinforcing previous findings that emphasize IBC's inhibitory properties on tumor cell proliferation. All chemical structures are shown in figure 1.

Synthetic Chalcones

Research on the molecular alteration of chalcone structures has enabled chemical variations that enhance both the physicochemical properties and the biological activities of chalcones. Common strategies for molecular modification include the organizational management of aryl rings, the substitution of alicyclic or steroidal scaffolds, aryl systems incorporating heteroaryl moieties and hybrid molecular frameworks. Structural modifications of chalcone structures primarily focus on the phenyl rings (A and B)[15].

The subsequent discussion examines the impact of organization activity association substitution configurations on the anticancer activity of chalcones such as the incorporation of electron contributing groups (-OH and -OCH_3), electron diminishing groups (-Cl, -Br and -F) and chalcone metal developments. The inclusion of hydroxyl and methoxy groups at detailed places on the phenyl rings has been shown to enhance the anticancer potency of synthetic chalcones. For example, 20-hydroxy-2,5-dimethoxychalcone (9, IC50/ 9.76-40.83μM) and 20-hydroxy-40,60-dimethoxychalcone (10, IC50/ 9.18/46.11 μM) exhibit antiproliferative and proapoptotic effects in various canine lymphoma and leukemia cell lines[40].

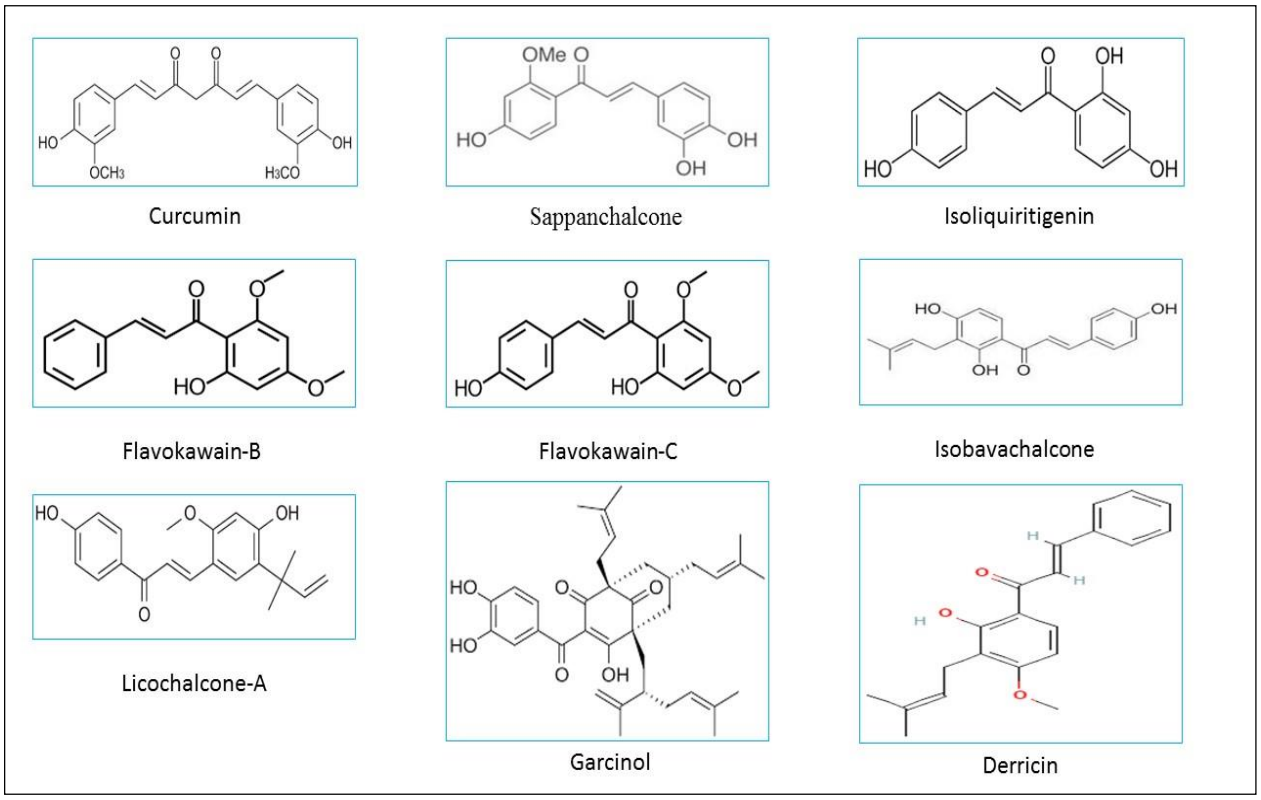

Figure 1: Basic Chemical Structure of various Natural sources for chalcones

Additionally, a series of halogenated chalcones (14, CC50/ 1.6/18.4µM) incorporating a halogen substituent (F, Cl, Br, etc.) within the core chalcone structure displayed significant cytotoxic effects and selective tumor toxicity.

Padhye and co-authors[24] reported that fluorinated chalcones (16, IC50/ 18.67 µM and 26.43 µM) established superior anti-oxidant and anti-proliferative movement against human pancreatic Bx/PC-3 cancer cells and human breast cancer BT-20 cells compared to their hydroxyl analogs. Chalcone–metal developments have also gained significant consideration in bioinorganic medicinal chemistry due to their coordination and synchronization possessions with several metals, as well as their modulatory possessions on multiple anticancer objectives.

Chalcone hybrids

Hybrid compounds take the probable to overwhelmed drug confrontation while exhibiting enhanced efficacy and improved specificity. Consequently, the integration of chalcone moieties with other anticancer pharmacophores offers a capable strategy in the progress of novel anticancer therapeutics[10]. Recent progress has led to the synthesis of numerous chalcone hybrids, which have been assessed for their anticancer activity. Several of these hybrids have demonstrated considerable effectiveness both *in vitro* and *in vivo*, highlighting their possible as promising anticancer agents. Artemisinin products which contain a peroxide-functionalized sesquiterpene lactone structure, are capable of generating extremely sensitive free radicals including peroxyl free radicals and ROS, in the occurrence of ferrous ions (Fe-II)[33]. Tumor cells exhibit significantly elevated levels of Fe-II compared to healthy cells, enabling artemisinin byproducts to produce peroxyl free radicals, ROS, oxidative stress, DNA impairment and discerning cell death in cancer cells. Thus, the hybridization of artemisinin and chalcone presents a probable approach for the progress of innovative anticancer agents that effectively induce noxiousness in cancer cells while preserving a high protection profile in usual cells. A series of artemisinin-lone hybrids (20, IC50/ 1.02–53.7 µM) has demonstrated substantial efficacy against intraerythrocytic *Plasmodium falciparum* parasites, along with notable activity against TK-10 (renal), UACC-62 (melanoma) and MCF-7 cancer cell lines[20].

A distinctive group of artemisinin-lone hybrids developed by Goel et al[12] exhibited significant effectiveness against HEPG-2 (hepatocellular carcinoma), PC-3 (prostate cancer), Mia PaCa-2 (pancreatic cancer), LS-180 (colon cancer) and HL-60 (leukemia) cancer cell lines, showing a high selectivity index. Azoles, a class of five-membered nitrogen-containing heterocyclic compounds, are distinguished by their electron rich nature. The diverse biological effects of chalcones suggest their potential to complicate targeted therapeutic interventions. Additionally, chalcone-based hybrids, including chalcone–indole, chalcone–ferrocene, chalcone–furan/thiophene, chalcone–pyridine/pyrimidine, chalcone–quinoline/quinolone, chalcone–quinoxaline/ quinazolinone, chalcone–quinone, chalcone–triazine and chalcone–dithiocarbamate, have also shown substantial anticancer activity.

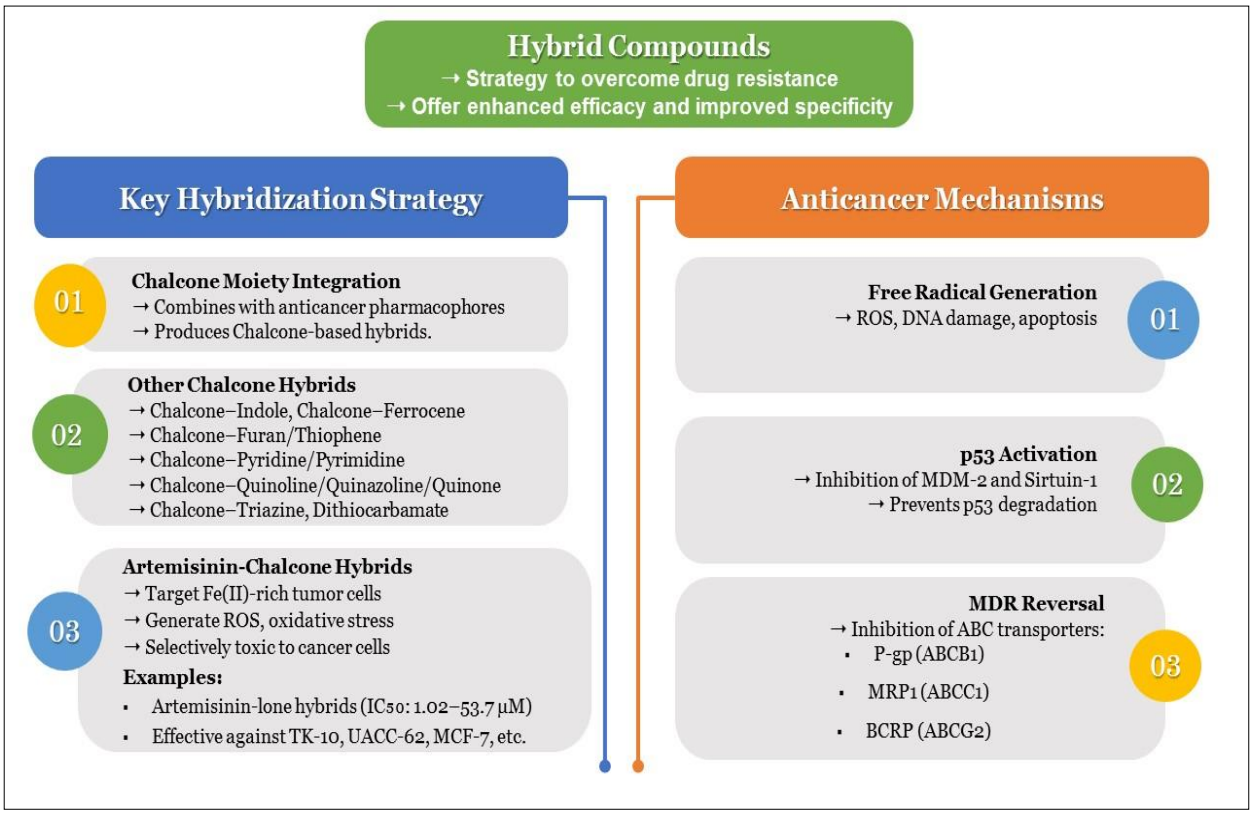

Figure 2: Chalcone Hybrids Compounds Strategy and Mechanisms

Various studies have focused on the mechanisms underlying the anticancer actions of chalcones which highlight their ability to interfere with cancer therapies, posing challenges for clinical applications. Consequently, accepting the appliances of action of chalcones and identifying their specific molecular objectives is essential for advancing the development of chalcone-based therapeutic agents. The tumor suppressor protein p53 is central in regulating the cell cycle and preserving cellular and genomic integrity, thereby precluding the formation of malignant cells. P5-3 is frequently targeted for deprivation by several factors including mouse double minute-2 (MDM-2) and Sirtuin-1 and inhibiting its degradation as a crucial approach in cancer therapy. MDM-2, an E3 ubiquitin ligase, acts as the primary negative regulator of p-53, promoting its monoubiquitination and subsequent proteasomal dilapidation in both the nucleus and cytoplasm[18].

Many chalcones tested have demonstrated the capability to inhibit key associates of the ATP-binding cassette (ABC) transporter family such as P-glycoprotein (P-gp, ABCB-1), MDR-associated protein 1 (MRP1, also known as ABCC1) and breast cancer resistance protein (BCRP, ABCG-2) as shown in figure 2. These transporters are primary contributors to MDR in cancer cells, further underscoring the potential of chalcones in overcoming chemotherapy resistance.

Chalcone based nanoparticle: A variety of nanoparticle established preparations containing chitosan, micelles, nanogels and polymeric nanoparticles, liposomes have remained industrialized demonstrating their potential value in addressing colon cancer through equally *in vitro* and *in vivo* studies. Also, inventive drug distribution systems have been introduced[11]. Alternative advanced approach evaluated for its therapeutic potential includes PEG-PE micelles coloaded with CUR and DOX, targeting HCT-116 human CRC cells using an anti-GLUT1 antibody[22]. This system demonstrated significant cytotoxic effects at short doses of DOX *in vitro*, surpassing non-targeted formulations and resulted in substantial tumor suppression and improved survival rates in female nude mice with established tumors.

Conclusion

In conclusion, chalcones exhibit significant potential as anticancer targets, demonstrating efficacy through diverse molecular mechanisms. Natural sources of chalcones including butein, CUR and xanthohumol, have shown promising anticancer properties. Advances in synthetic chalcones and chalcone hybrids have enabled structural modifications to enhance potency and selectivity.

Furthermore, chalcone-based nanoparticles offer innovative drug delivery solutions, improving bioavailability and therapeutic efficiency. This review highlights the importance of chalcones in cancer therapy, addressing gaps in previous studies. Future research should focus on optimizing chalcone derivatives and nanoparticle formulations to develop clinically viable anticancer agents, contributing to more effective and targeted cancer treatments.

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