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Advance Therapeutical Use Of Chalcone Derivatives in The Field of Anticancer Drug Discovery

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Abstract

Chalcones, a versatile class of open-chain, or close chain flavonoids (1,3diaryl-2-propen-1-ones), have gained significant attention in recent years for their promising role in anticancer drug discovery. Their simple synthetic accessibility, structural flexibility, and ability to interact with multiple molecular targets make them attractive scaffolds in medicinal chemistry. Numerous studies have demonstrated that chalcone derivatives exhibit potent anticancer activity through mechanisms such as induction of apoptosis, disruption of tubulin polymerization, inhibition of angiogenesis, and modulation of signaling pathways including NF-κB, PI3K/Akt, and MAPK. Furthermore, the incorporation of different substituent (methoxy, hydroxyl, halogens, heterocycles) has been shown to enhance selectivity and efficacy against diverse cancer cell lines. Recent advances also highlight the synergistic potential of chalcone-based metal complexes, which often demonstrate superior cytotoxicity compared to free ligands. Computational tools such as molecular docking and density functional theory (DFT) further aid in understanding the structure–activity relationship and predicting binding affinities with cancer-related proteins. This review emphasizes the multifaceted role of chalcone derivatives in anticancer therapy, focusing on their synthetic strategies, mechanistic insights, biological activity, and future prospects in drug development.Chalcone are common simple chemical scaffolds found in many naturally occurring compound. many chalcone derivatives were also prepared due to their convenient synthesis

Keywords: Chalcone derivatives, anticancer therapy, apoptosis, angiogenesis, metal complexes, signaling pathways, computational studies.

Introduction

Cancer remains one of the leading causes of mortality worldwide, accounting for millions of deaths each year. Despite advances in chemotherapeutic regimens and targeted therapies, the development of drug resistance, toxicity to normal cells, and limited selectivity of current agents continue to pose significant challenges. Consequently, there is a growing need to identify and develop novel molecules with improved safety profiles and enhanced therapeutic potential. In this context, **chalcone derivatives** have emerged as promising candidates in the field of anticancer drug discovery. Chalcones (1,3-diaryl-2-propen-1-ones) are naturally occurring precursors of flavonoids and isoflavonoids, widely distributed in edible plants such as licorice, apples, and various spices. Structurally, chalcones consist of two aromatic rings (A and B) linked by an α,β-unsaturated carbonyl system, which provides a reactive pharmacophore capable of engaging in diverse biochemical interactions. This unique scaffold allows easy modification of substituents on either aromatic ring, leading to a wide array of derivatives with distinct biological activities.

The pharmacological interest in chalcones is largely attributed to their ability to modulate multiple cellular targets simultaneously, a feature highly advantageous in combating complex diseases such as cancer. Several synthetic and naturally derived chalcones have demonstrated potent cytotoxic activity against breast,

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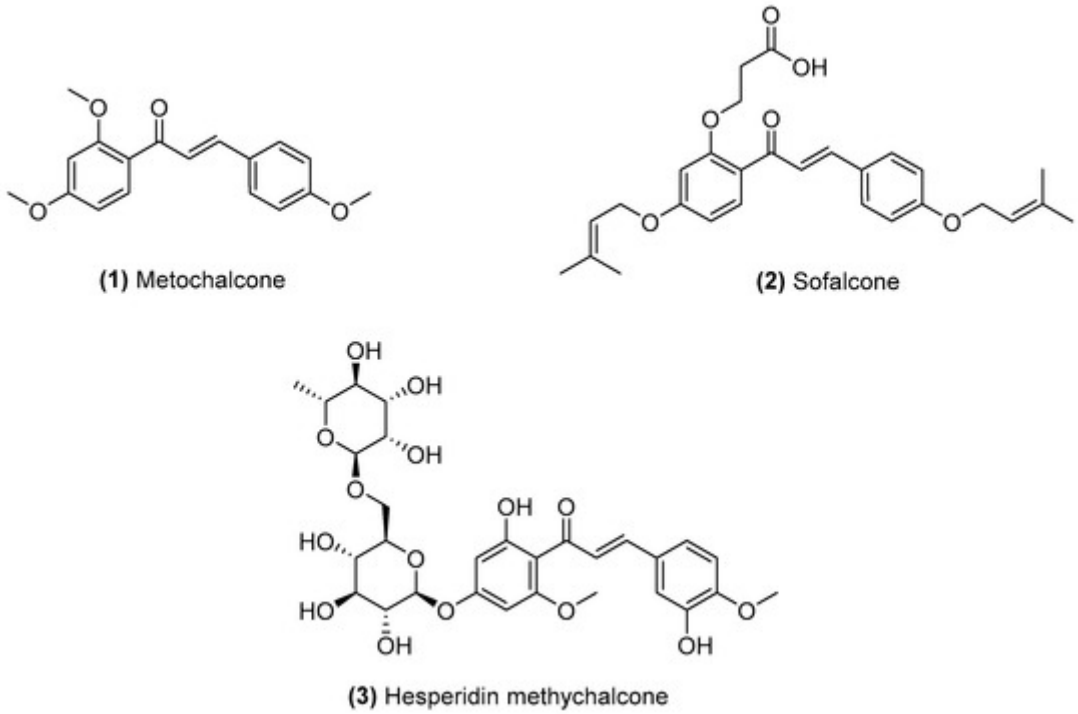
lung, colon, prostate, liver, and leukemia cell lines. Mechanistic studies suggest that chalcones exert their anticancer effects by inducing programmed cell death (apoptosis), inhibiting microtubule assembly, blocking angiogenic pathways, and interfering with critical oncogenic signaling cascades. Importantly, chalcones often exhibit selective toxicity toward cancer cells while sparing normal tissues, underscoring their therapeutic relevance.

In addition to free chalcones, their **metal complexes** (with transition metals such as copper, nickel, iron, and rhodium) have shown enhanced anticancer properties due to improved stability, lipophilicity, and ability to generate reactive oxygen species (ROS). These complexes not only increase cytotoxic potency but may also overcome multidrug resistance in cancer cells. Moreover, computational approaches including **molecular docking, QSAR, and DFT calculations** provide deeper insights into binding interactions, electronic distribution, and structure–activity relationships of chalcone derivatives, thereby facilitating rational design of potent anticancer agents.Given their broad pharmacological profile and chemical tunability, chalcones represent a versatile platform for the development of next-generation anticancer therapeutics. This paper aims to provide a comprehensive overview of chalcone derivatives in anticancer therapy, covering their synthesis, biological mechanisms, role of metal complexes, computational studies, and future perspectives in oncology.

Exemplifying the clinical potential of chalcones

(**Figure 1**).



Section 2: Synthesis and Structural Modifications of Chalcone Derivatives

- Different synthetic approaches (Claisen–Schmidt condensation, green synthesis, microwave-assisted, ionic liquids).
- Substituent effects (–OH, –OCH_3, halogens, heterocycles, ferrocenyl, thiophene groups,).

And some other electron donating and electron withdrawing group on chalcone

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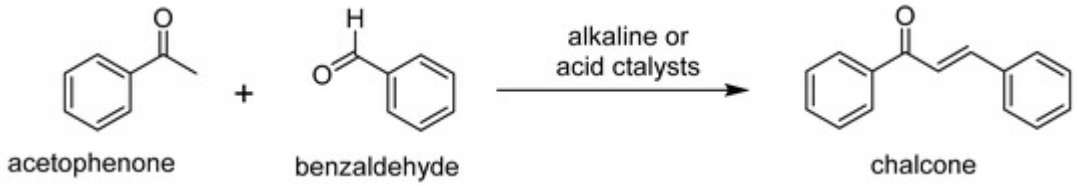
- How modifications improve **anticancer activity and selectivity**.

2. Synthesis and Structural Modifications of Chalcone Derivatives

Chalcones (1,3-diaryl-2-propen-1-ones) are relatively simple to synthesize, which makes them an attractive scaffold for medicinal chemists. Their structural flexibility allows extensive modification at different positions of the aromatic rings, leading to a wide library of derivatives with improved pharmacological properties. The core structure contains an **α,β-unsaturated carbonyl group**, which serves as a reactive pharmacophore and plays a critical role in anticancer activity. Several conventional and modern synthetic strategies have been employed to obtain chalcones and their substituted analogs.

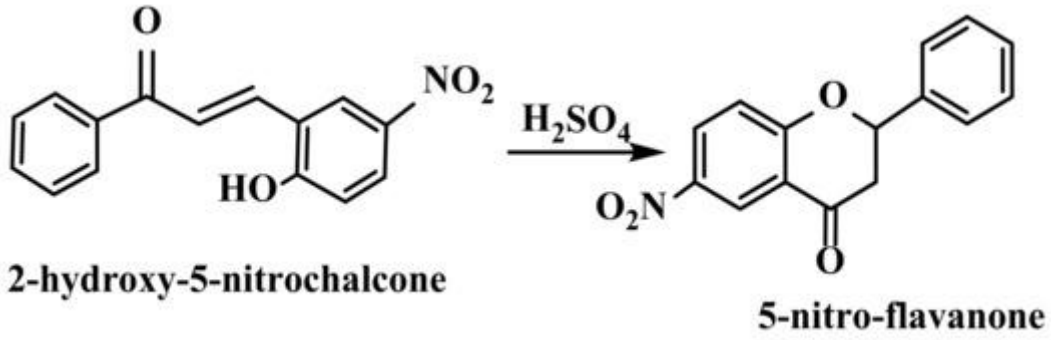
Figure 2. Structural of chalcone scaffold.



(Figure 3).

(E)-Chalcone (Z)-Chalcone

acetophenone derivative. This method is highly versatile, providing good yields of chalcones under mild reaction conditions. Bases such as NaOH, KOH, or Na_2CO_3 are commonly used, while organic solvents (ethanol, methanol) or water serve as reaction media. Although efficient, this method often requires longer reaction times and may generate by-products.we can change the reactivity of chalcone by replace hydrogen with the help of other electron withdrawing or electron releasing group because the structure of chalcone is flexible obtained 5-nitro-flavanones by refluxing 2 hydroxychalcones in presence of concentrated sulfuric acid



Due to their flexible structure, chalcones can effectively bind to many enzymes and receptors, which explains the many biological applications of these compounds . Another explanation for pharmacological activities of

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these compounds is conjugation between double bond and carbonyl group present in structure. Bioactivities of chalcones are dependent on the position, number, and nature of substituents on the two aromatic residues (aldehyde and acetophenone

2.2 Green and Environment-Friendly Approaches

To minimize environmental impact and align with green chemistry principles, researchers have developed eco-friendly synthetic protocols. **Solvent-free reactions, microwave irradiation, ultrasound-assisted synthesis, and the use of ionic liquids or heterogeneous catalysts** have emerged as sustainable alternatives. Microwave-assisted synthesis, in particular, has gained popularity due to its ability to reduce reaction time drastically (from hours to minutes) and improve product yields. Solvent-free methods further eliminate toxic waste, making them attractive for large-scale production of bioactive chalcones.

2.3 Substituent Effects and Structure–Activity Relationships

The anticancer potential of chalcones can be tuned by introducing various substituents on the aromatic rings. Hydroxyl and methoxy groups on the **A-ring** generally enhance hydrogen-bonding interactions with target proteins, while halogen substituents (Cl, Br, F) on the **B-ring** often increase lipophilicity and cellular uptake. Incorporation of **heterocyclic moieties** (such as thiophene, pyridine, or imidazole) improves binding affinity toward enzymes involved in cancer progression. In recent years, **ferrocenyl-substituted chalcones** have shown notable anticancer effects owing to their redox properties and ability to generate reactive oxygen species within tumor cells.

2.4 Hybrid Chalcone Derivatives

Designing chalcones as hybrid molecules by combining them with known pharmacophores has also been explored. For instance, chalcone–triazole hybrids, chalcone–coumarin hybrids, and chalcone–quinoline hybrids have demonstrated improved cytotoxicity against breast, colon, and lung cancer cell lines. Such structural modifications not only broaden the spectrum of biological activity but also help overcome limitations such as low solubility or poor metabolic stability.

2.5 Examples of Potent Synthetic Chalcones

Numerous synthetic chalcones have entered preclinical studies as potential anticancer candidates. For example, **2′-hydroxy-4′-methoxychalcone** and **licochalcone A** exhibited strong inhibitory

activity against breast and prostate cancer cells. Methoxy-substituted chalcones were found to block tubulin polymerization, while nitro-substituted derivatives induced apoptosis via mitochondrial pathways. These findings highlight the importance of rational structural modification in optimizing chalcone-based anticancer agents.

3. Mechanisms of Anticancer Activity of Chalcone Derivatives

The anticancer potential of chalcone derivatives arises from their ability to target multiple cellular pathways simultaneously. Unlike conventional chemotherapeutic agents that often act on a single protein, chalcones exhibit a “multi-target” profile, enabling them to interfere with cancer progression at different molecular levels. Several mechanisms have been elucidated, highlighting their role in apoptosis induction, cell cycle modulation, angiogenesis inhibition, and disruption of oncogenic signaling pathways.

3.1 Induction of Apoptosis

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Apoptosis, or programmed cell death, is a natural defense mechanism against uncontrolled cell proliferation. Many chalcone derivatives have been reported to trigger apoptosis in cancer cells through both **intrinsic (mitochondrial)** and **extrinsic (death receptor-mediated)** pathways.

- In the intrinsic pathway, chalcones disrupt the mitochondrial membrane potential, leading to the release of cytochrome c, activation of caspase-9, and subsequent activation of executioner caspases such as caspase-3.
- In the extrinsic pathway, chalcones upregulate death receptors (e.g., Fas, TRAIL receptors), leading to caspase-8 activation.

Examples include **butein** and **xanthohumol**, which induce apoptosis in breast and colon cancer cells via caspase-dependent mechanisms. Some chalcones also enhance reactive oxygen species (ROS) production, which further amplifies apoptotic signaling.

3.2 Cell Cycle Arrest

Chalcones can inhibit cancer cell proliferation by blocking cell cycle progression at specific checkpoints.

- Hydroxylated chalcones have been shown to cause **G2/M phase arrest**, primarily through inhibition of cyclin B1/CDK1 complexes.
- Methoxy-substituted chalcones often cause **G0/G1 arrest**, reducing cyclin D1 and CDK4 expression.

By halting uncontrolled mitosis, chalcones limit tumor growth and sensitize cancer cells to apoptosis-inducing agents.

3.3 Inhibition of Angiogenesis

Angiogenesis, the formation of new blood vessels, is essential for tumor survival and metastasis. Several chalcone derivatives suppress angiogenesis by targeting vascular endothelial growth factor (VEGF) signaling.

- **Xanthohumol** and synthetic halogenated chalcones inhibit VEGF-induced proliferation of endothelial cells.
- Chalcones also downregulate **matrix metalloproteinases (MMP-2 and MMP-9)**, enzymes involved in extracellular matrix remodeling, thereby limiting tumor invasion.

This antiangiogenic property enhances their potential as anti-metastatic agents.

3.4 Modulation of Oncogenic Signaling Pathways

Chalcones interfere with multiple intracellular signaling cascades that are critical for cancer cell survival and proliferation.

- **NF-κB Pathway**: Chalcones block the nuclear translocation of NF-κB, reducing the expression of anti-apoptotic proteins such as Bcl-2 and survivin.
- **PI3K/Akt Pathway**: Some derivatives inhibit Akt phosphorylation, leading to reduced cell survival and increased apoptosis.
- **MAPK Pathway**: Chalcones modulate ERK, JNK, and p38 signaling, influencing both apoptotic and proliferative responses.

By modulating these interconnected pathways, chalcones exert broad-spectrum anticancer effects and may overcome resistance to conventional drugs.

3.5 Targeting Tubulin Polymerization

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Microtubules are essential for cell division, and their disruption is a validated anticancer strategy. Several synthetic chalcones, particularly methoxy-substituted derivatives, bind to the **colchicine-binding site of tubulin**, thereby preventing microtubule assembly. This results in mitotic arrest and subsequent apoptosis. Some chalcone analogs have shown comparable activity to established tubulin inhibitors such as colchicine and combretastatin.

3.6 Overcoming Multidrug Resistance

Drug resistance remains a major hurdle in cancer therapy. Chalcones have demonstrated the ability to inhibit **P-glycoprotein (P-gp)**, a drug efflux pump responsible for reducing intracellular drug concentrations. By modulating P-gp activity, chalcones enhance the intracellular retention of chemotherapeutic agents, thereby resensitizing resistant cancer cells to treatment.

4. Role of Chalcone Metal Complexes in Anticancer Therapy

While free chalcones display remarkable anticancer activity, their clinical application is sometimes limited by **poor solubility, rapid metabolism, and modest bioavailability**. To address these limitations, coordination of chalcone ligands with transition metals has emerged as a promising strategy. Metal complexation not only enhances the stability and lipophilicity of chalcones but also introduces additional mechanisms of cytotoxicity, such as **generation of reactive oxygen species (ROS), DNA binding, and enzyme inhibition**. Among transition metals, copper, nickel, rhodium, and iron complexes of chalcones have been most extensively studied.

4.1 Copper Complexes

Copper is an essential trace element involved in several enzymatic processes, and its complexes are known for redox activity. **Copper–chalcone complexes** exhibit enhanced cytotoxicity against breast, liver, and colon cancer cells compared to free ligands.

- These complexes promote apoptosis through mitochondrial dysfunction and caspase activation.
- Their redox cycling ability enables production of ROS, which damages DNA and triggers cell death.
- Some copper–chalcone complexes also inhibit **topoisomerase II**, a key enzyme involved in DNA replication, thereby preventing tumor growth.

4.2 Nickel Complexes

Nickel–chalcone complexes have demonstrated significant anticancer activity, particularly through **DNA intercalation** and disruption of replication machinery.

- Ni(II) chalcone complexes often display **higher lipophilicity**, facilitating cellular uptake.
- They interfere with **cell cycle progression** and induce apoptosis in lung and breast cancer cells.
- Some studies suggest that nickel coordination enhances selectivity toward tumor cells over normal cells, making them potential candidates for targeted therapy.

4.3 Rhodium Complexes

Rhodium-based complexes are gaining attention as alternatives to platinum drugs due to their **lower toxicity and unique binding properties**.

- **Rhodium–chalcone complexes** can bind to DNA through intercalation and groove binding, leading to structural distortion of the double helix.

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- These complexes also inhibit critical enzymes such as **tyrosine kinases**, thereby interfering with oncogenic signaling pathways.
- Importantly, rhodium complexes show potential to overcome platinum resistance in certain cancer cell lines.

The combination of rhodium's coordination chemistry and chalcone's reactive pharmacophore creates a synergistic effect that amplifies anticancer activity.

4.4 Iron and Ferrocenyl Complexes

Incorporation of iron, particularly in the form of **ferrocenyl-substituted chalcones**, introduces unique redox behavior that significantly boosts anticancer efficacy.

- Ferrocenyl chalcones undergo redox cycling, producing ROS that selectively damage tumor cells due to their higher oxidative stress levels compared to normal cells.
- These complexes also disrupt mitochondrial function and enhance DNA cleavage.
- Importantly, ferrocenyl chalcones often retain good biocompatibility, making them attractive scaffolds for anticancer drug design.

4.5 Comparative Advantages of Metal Complexation

Overall, chalcone metal complexes demonstrate several advantages over free chalcones:

1. **Enhanced Cytotoxicity** – due to combined action of metal and organic ligand.
2. **Improved Pharmacokinetics** – increased lipophilicity and stability.
3. **Multimodal Mechanisms** – apoptosis, ROS generation, DNA binding, enzyme inhibition.
4. **Potential to Overcome Resistance** – especially in rhodium and copper complexes.

These properties highlight the importance of metal–chalcone coordination in designing next-generation anticancer therapeutics

5. Computational Insights into Chalcone Anticancer Activity

Computational chemistry has become a cornerstone in modern drug discovery, providing valuable information about **molecular interactions, electronic properties, and structure–activity relationships (SARs)**. For chalcone derivatives, computational studies play a critical role in predicting biological targets, optimizing substituents, and understanding their mechanisms at the molecular level. Techniques such as **molecular docking, quantitative structure–activity relationship (QSAR), and density functional theory (DFT)** are frequently employed to support experimental findings and guide the synthesis of more potent chalcone analogs.

5.1 Molecular Docking Studies

Molecular docking is widely used to predict how chalcone derivatives interact with key cancer-related proteins.

- Docking studies have shown that chalcones can effectively bind to the **ATP-binding pocket of kinases**, thereby inhibiting phosphorylation events essential for cancer cell survival.
- Several chalcones exhibit strong affinity toward **tubulin at the colchicine-binding site**, consistent with their ability to inhibit microtubule polymerization.

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- Docking with **NF-κB and PI3K/Akt signaling proteins** revealed hydrogen bonding and π–π stacking interactions, supporting experimental evidence of pathway inhibition.

Through docking simulations, researchers can identify promising substituents that improve binding energy and enhance selectivity toward cancer targets.

5.2 QSAR and Pharmacophore Modeling

Quantitative structure–activity relationship (QSAR) studies have been extensively applied to chalcone derivatives.

- QSAR models highlight the importance of **electron-donating groups (–OH, –OCH_3)** on the A-ring in improving cytotoxicity.
- Halogen substitution on the B-ring increases hydrophobic interactions with protein targets, enhancing activity.
- Pharmacophore mapping often identifies the **α,β-unsaturated carbonyl group** as an essential pharmacophore, acting as a Michael acceptor for nucleophilic residues in proteins.

These models provide predictive frameworks that accelerate the identification of active chalcone scaffolds before laboratory synthesis.

5.3 Density Functional Theory (DFT) Studies

DFT calculations are useful for understanding the electronic structure and reactivity of chalcones.

- **HOMO–LUMO gap analysis** indicates that derivatives with smaller energy gaps are more reactive and often show higher biological activity.
- Molecular electrostatic potential (MEP) maps help identify electrophilic and nucleophilic regions that interact with biomolecules.
- DFT also provides insights into conformational stability, which correlates with binding affinity in docking studies.

For example, DFT studies revealed that ferrocenyl chalcones possess lower HOMO–LUMO gaps, explaining their enhanced redox activity and superior anticancer potency.

5.4 Integration of In Silico and In Vitro Studies

A combined approach using computational and experimental techniques offers the most powerful insights.

- Docking predictions often correlate well with **in vitro cytotoxic assays**, validating the reliability of computational models.
- Computational optimization reduces time and cost by narrowing down potential lead compounds before chemical synthesis.
- Recent advances in **molecular dynamics (MD) simulations** further refine predictions by evaluating the stability of chalcone–protein complexes over time.

5.5 Future Prospects of Computational Approaches The application of **artificial intelligence (AI) and machine learning** in QSAR modeling is expected to revolutionize chalcone research. Predictive algorithms can analyze large chemical libraries and suggest optimal modifications for anticancer activity. Combining **DFT, docking, and machine learning** will accelerate the discovery of chalcone-based anticancer drugs with high efficacy and minimal side effects. **6. Pharmacological and Environmental Considerations**

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The successful translation of chalcone derivatives from laboratory synthesis to clinical application depends not only on their anticancer efficacy but also on their **pharmacological properties, safety profiles, and environmental sustainability**. While many chalcones show potent in vitro activity, issues such as low solubility, rapid metabolism, and off-target effects must be addressed to improve their clinical potential. At the same time, the synthetic routes used to prepare chalcones and their complexes should follow principles of **green chemistry** to minimize environmental hazards.

6.1 ADMET Properties

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) studies are critical for evaluating chalcone derivatives as drug candidates.

- **Absorption**: Chalcones are generally lipophilic, which favors passive absorption across cell membranes. However, excessive hydrophobicity can reduce water solubility, limiting oral bioavailability.
- **Distribution**: Some chalcones demonstrate preferential accumulation in tumor tissues due to their affinity for cancer-specific transporters.
- **Metabolism**: Chalcones undergo phase I and phase II metabolism in the liver, mainly via hydroxylation, glucuronidation, and sulfation. This rapid metabolism can shorten half-life.
- **Excretion**: Most chalcone metabolites are excreted through urine or bile, often reducing systemic toxicity.
- **Toxicity**: Chalcones generally exhibit low toxicity in normal cells. However, certain derivatives with strong electrophilic groups may cause oxidative stress or hepatotoxicity at high doses. Careful structural optimization is therefore essential to balance efficacy and safety.

6.2 Strategies to Improve Pharmacological Profiles

Several approaches have been developed to overcome pharmacokinetic limitations:

- **Prodrug Design**: Conjugation of chalcones with amino acids or peptides enhances solubility and stability.
- **Nanocarrier Systems**: Encapsulation of chalcones in liposomes, polymeric nanoparticles, or solid lipid nanoparticles improves bioavailability and enables targeted delivery.
- **Metal Complexation**: As discussed earlier, coordination with transition metals such as Cu, Ni, Rh, or Fe increases lipophilicity and cytotoxicity while improving metabolic stability.
- **Hybrid Molecules**: Linking chalcones with established pharmacophores (e.g., triazole, coumarin) can enhance both pharmacodynamics and pharmacokinetics.

These strategies collectively improve the likelihood of chalcones progressing into clinical trials.

6.3 Safety and Selectivity

One of the notable advantages of chalcones is their tendency to exhibit **selective cytotoxicity toward cancer cells** while sparing normal tissues. This selectivity is often attributed to:

- Higher oxidative stress in cancer cells, making them more susceptible to ROS generation by chalcones.
- Overexpression of certain transporters in tumor cells that enhance chalcone uptake.
- Differential activation of apoptotic pathways in malignant cells compared to healthy cells.

Nevertheless, long-term toxicological studies and in vivo evaluations are essential before clinical translation.

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6.4 Environmental Aspects and Green Chemistry

The increasing demand for eco-friendly pharmaceutical processes has motivated researchers to develop **sustainable synthetic methods** for chalcone derivatives.

- **Solvent-free and microwave-assisted syntheses** reduce energy consumption and hazardous waste.
- Use of **biocatalysts and ionic liquids** provides safer alternatives to conventional organic solvents.
- Incorporating **renewable feedstocks** in synthesis minimizes the environmental footprint.

Furthermore, the biodegradability of chalcones is generally favorable, reducing concerns of long-term environmental accumulation compared to synthetic drugs with persistent residues. However, metal–chalcone complexes require special attention since improper disposal of transition-metal-containing compounds may pose ecological risks.

6.5 Balancing Therapeutic and Environmental Goals

Future chalcone research should prioritize dual objectives:

1. **Therapeutic Optimization** – ensuring strong anticancer efficacy, favorable ADMET properties, and low toxicity.
2. **Sustainable Chemistry** – adopting environmentally benign synthesis, energy-efficient processes, and safer catalysts.

By integrating pharmacological and environmental considerations, chalcone derivatives can be developed as not only effective but also responsible candidates for modern anticancer therapy.

7. Conclusion and Future Perspectives

Chalcone derivatives represent a highly versatile and promising class of compounds in the search for effective anticancer therapeutics. Their **simple structural framework**, ease of modification, and ability to target multiple molecular pathways make them attractive scaffolds for drug discovery. Extensive studies have confirmed their role in inducing apoptosis, arresting the cell cycle, inhibiting angiogenesis, modulating oncogenic signaling cascades, and disrupting tubulin polymerization. Importantly, chalcones often display selective cytotoxicity toward malignant cells, reducing the risk of damage to healthy tissues compared to conventional chemotherapeutic agents.

The incorporation of **structural modifications** such as hydroxyl, methoxy, halogen, heterocyclic, or ferrocenyl substituents further enhances anticancer potency and selectivity. Additionally, **metal complexes of chalcones**—notably those with copper, nickel, rhodium, and iron—have shown superior cytotoxic activity through synergistic effects of metal coordination and organic pharmacophores. These complexes improve solubility, lipophilicity, and metabolic stability, while introducing additional mechanisms such as ROS generation and DNA binding.

Computational tools including **molecular docking, QSAR, and DFT studies** have greatly contributed to understanding structure–activity relationships and predicting interactions with biological targets. Integration of **in silico, in vitro, and in vivo approaches** ensures a rational pipeline for chalcone-based drug design. The rise of artificial intelligence and machine learning promises to further accelerate this process by predicting optimal modifications with high precision.

From a **pharmacological perspective**, challenges remain in terms of bioavailability, metabolic stability, and long-term safety. Approaches such as **nanocarrier delivery systems, prodrug design, and hybrid chalcone**

derivatives offer viable strategies to overcome these limitations. At the same time, the adoption of **green chemistry principles** in chalcone synthesis ensures that their development aligns with environmental sustainability.

Looking ahead, chalcone derivatives and their metal complexes hold immense potential as **next-generation anticancer agents**. Future research should focus on:

- Conducting more **preclinical and clinical trials** to establish efficacy and safety in humans.
- Exploring **synergistic effects with existing chemotherapeutics** to reduce drug resistance.
- Expanding the use of **computational and AI-driven approaches** to design novel chalcone analogs.
- Balancing **therapeutic efficacy with environmental responsibility**, ensuring sustainable synthesis and safe disposal of metal-containing compounds.

In conclusion, chalcone derivatives embody a unique combination of **chemical flexibility, biological efficacy, and environmental adaptability**. With continued interdisciplinary research, they are poised to contribute significantly to the development of safe, effective, and sustainable anticancer therapies.

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