Microwave-Assisted Green Synthesis and Anticancer Potential of Chromene–1,2,4-Oxadiazole Hybrids in Breast Cancer Therapy: Recent Advances and Future Perspectives

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***Abstract*—Polyherbal foot care cooling gel is a topical herbal formulation developed to provide cooling, soothing, moisturizing, refreshing, and antimicrobial effects for tired, stressed, and unhealthy feet. Feet are continuously exposed to environmental pollutants, excessive sweating, heat, friction, and microbial contamination due to daily activities such as walking, prolonged standing, and use of closed footwear. These conditions may lead to dryness, irritation, unpleasant odor, burning sensation, cracked heels, fungal infections, and foot fatigue. Proper foot care is therefore essential for maintaining hygiene, comfort, and skin health. Herbal formulations have gained significant importance in recent years because they are considered safer, more economical, and associated with fewer side effects compared to synthetic preparations. Polyherbal formulations are especially beneficial because the combined action of different medicinal plants produces synergistic therapeutic effects.**

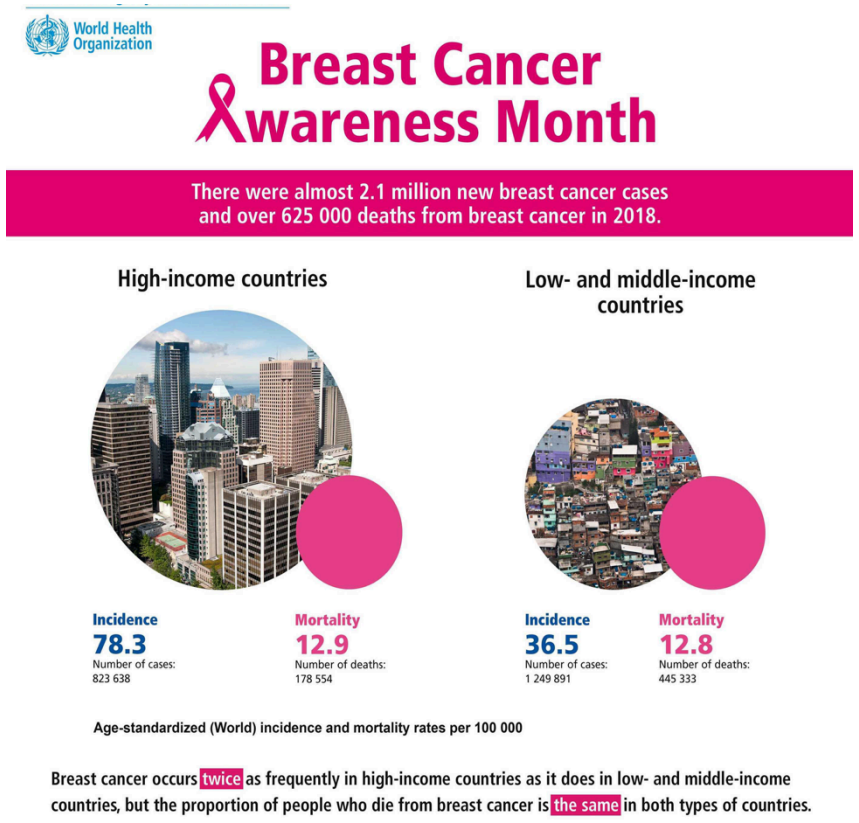
The present study focuses on the formulation and evaluation of a polyherbal foot care cooling gel using natural herbal ingredients such as peppermint extract, aloe vera gel, neem extract, vetiver extract, almond oil, Carbopol 934, sodium benzoate, and purified water. Carbopol 934 was used as a gelling agent to provide appropriate viscosity, consistency, and stability to the formulation. Peppermint extract, rich in menthol, was incorporated to produce an immediate cooling and refreshing sensation that helps relieve foot fatigue and discomfort. Aloe vera gel was included because of its excellent moisturizing, soothing, anti-inflammatory, and skin-protective properties. Neem extract is widely known for its antimicrobial, antifungal, and antibacterial activities, which help prevent foot infections, itching, and unpleasant odor. Vetiver extract contributes cooling and calming effects along with a pleasant aroma, while almond oil acts as a nourishing emollient that softens and hydrates dry skin. Sodium benzoate was added as a preservative to protect the formulation from microbial contamination and improve shelf life.

The gel was prepared by dispersing Carbopol 934 in water followed by incorporation of herbal extracts and other ingredients with continuous stirring to obtain a smooth and homogeneous preparation. The prepared formulation was evaluated for various physicochemical parameters including appearance, color, odor, pH, viscosity, spreadability, homogeneity, washability, cooling effect, skin feel, and stability. The formulation showed satisfactory physical characteristics with smooth texture, pleasant odor, and good consistency. The pH of the gel was found to be compatible with skin, indicating suitability for topical application without causing irritation. The gel exhibited good spreadability and was easily washable, enhancing patient convenience and compliance.

The cooling effect produced by peppermint and vetiver extracts provided instant freshness and relief from foot fatigue. Aloe vera and almond oil improved skin hydration and softness, preventing dryness and roughness of the feet. Neem extract contributed antimicrobial protection, which may help reduce microbial growth responsible for foot odor and infections. The prepared formulation remained stable during storage and did not show significant changes in color, consistency, or phase separation. The gel was non-greasy, non-sticky, and aesthetically acceptable, making it suitable for routine use.

***Index Terms*—Polyherbal gel, Foot care, Cooling gel, Herbal formulation, Peppermint extract, Aloe vera gel, Neem extract, Vetiver extract, Carbopol 934, Antimicrobial activity, Moisturizing effect, Topical preparation, Herbal cosmetics, Skin care, Foot hygiene**

I. Introduction



Cancer is one of the leading causes of morbidity and mortality worldwide and represents a substantial public health challenge. According to recent global epidemiological analyses, cancer incidence and mortality are steadily increasing due to aging populations, urbanization, sedentary lifestyles, environmental exposure, and genetic susceptibility [1,4]. Breast cancer is currently the most commonly diagnosed cancer among women globally and accounts for a significant proportion of cancer-related deaths [9,12].

Recent advances in cancer biology have revealed that breast cancer progression involves complex interactions among oncogenic signaling pathways, epigenetic dysregulation, immune evasion, angiogenesis, metabolic reprogramming, and tumor microenvironment modulation [6,7]. Despite significant progress in targeted therapeutics and precision medicine, chemotherapy-associated toxicity, multidrug resistance, tumor recurrence, and metastasis remain major therapeutic limitations [5,13,14].

Heterocyclic compounds constitute an important class of pharmacologically active molecules in medicinal chemistry because of their remarkable structural versatility and biological activity [15]. Among them, chromene derivatives have attracted substantial interest owing to their anticancer, anti-inflammatory, antimicrobial, antioxidant, and kinase inhibitory properties [18]. Similarly, the 1,2,4-oxadiazole scaffold is recognized as a privileged heterocyclic pharmacophore with potent anticancer activity, metabolic stability, and favorable pharmacokinetic properties.

The concept of molecular hybridization, involving the integration of two or more bioactive pharmacophores into a single molecular framework, has emerged as an effective strategy for improving therapeutic efficacy

and minimizing adverse effects. Chromene–1,2,4-oxadiazole hybrids have demonstrated promising antiproliferative activity against breast cancer cell lines through modulation of EGFR signaling pathways, induction of apoptosis, cell cycle arrest, and inhibition of metastasis [17,19].

Simultaneously, green chemistry has become increasingly important in pharmaceutical synthesis due to growing environmental concerns and the demand for sustainable manufacturing processes. Microwave-assisted organic synthesis has emerged as an efficient, rapid, and eco-friendly synthetic approach characterized by shorter reaction times, enhanced yields, reduced solvent utilization, and improved energy efficiency [16].

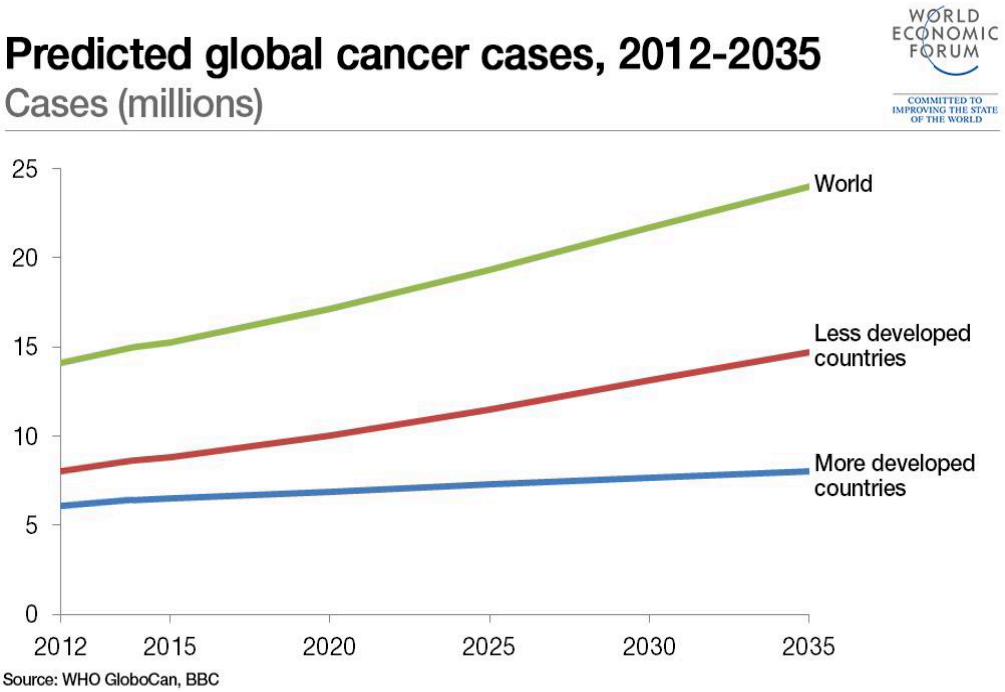
Therefore, the present review focuses on the microwave-assisted green synthesis of chromene–1,2,4-oxadiazole hybrids and their emerging role as potential anticancer agents for breast cancer therapy.

II. Global Burden of Breast Cancer

Breast cancer represents a major healthcare burden worldwide. According to global cancer statistics, breast cancer surpassed lung cancer as the most commonly diagnosed cancer globally, accounting for approximately 2.3 million new cases annually [1]. Mortality rates remain particularly high in low- and middle-income countries due to delayed diagnosis, inadequate healthcare infrastructure, and limited access to targeted therapies [2].

The incidence of breast cancer varies geographically due to differences in genetic predisposition, reproductive patterns, hormonal exposure, obesity, alcohol consumption, and lifestyle-associated risk factors [3,10]. Emerging evidence suggests that inherited mutations in BRCA1 and BRCA2 genes significantly contribute to breast cancer susceptibility and prognosis [11].

Recent projections indicate that the global cancer burden may increase substantially by 2050, emphasizing the urgent need for innovative therapeutic interventions and sustainable drug development approaches [4].

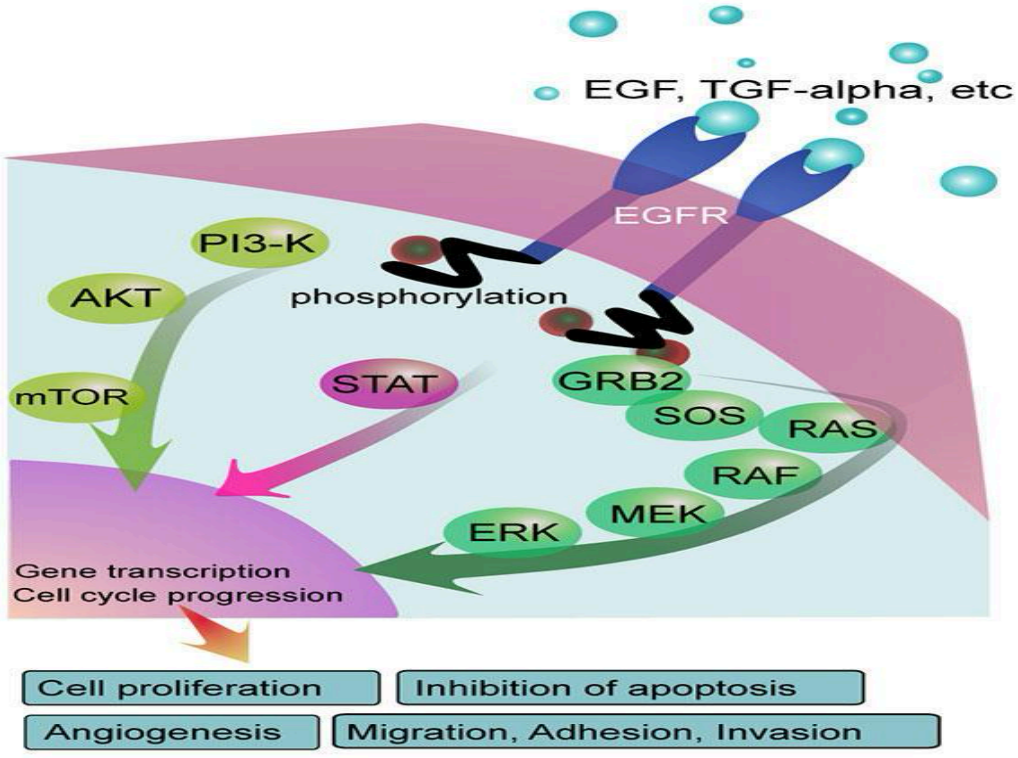


III. Molecular Biology and Hallmarks of Breast Cancer

Breast cancer development involves multiple genetic and epigenetic alterations that disrupt normal cellular homeostasis. Hanahan's updated hallmarks of cancer include sustained proliferative signaling, resistance to apoptosis, immune evasion, metabolic reprogramming, phenotypic plasticity, and genomic instability [6].

Key molecular pathways implicated in breast cancer include:

- EGFR signaling pathway
- PI3K/AKT/mTOR pathway
- RAS/RAF/MEK/ERK pathway
- HER2-mediated signaling
- Estrogen receptor signaling
- p53 tumor suppressor pathway



Epigenetic modifications such as DNA methylation, histone acetylation, and microRNA dysregulation also contribute significantly to tumor progression and therapeutic resistance [7].

EGFR overexpression is associated with aggressive tumor phenotypes, increased proliferation, angiogenesis, and poor prognosis in breast cancer. Consequently, EGFR inhibition has become an important therapeutic target for novel anticancer agents [17].

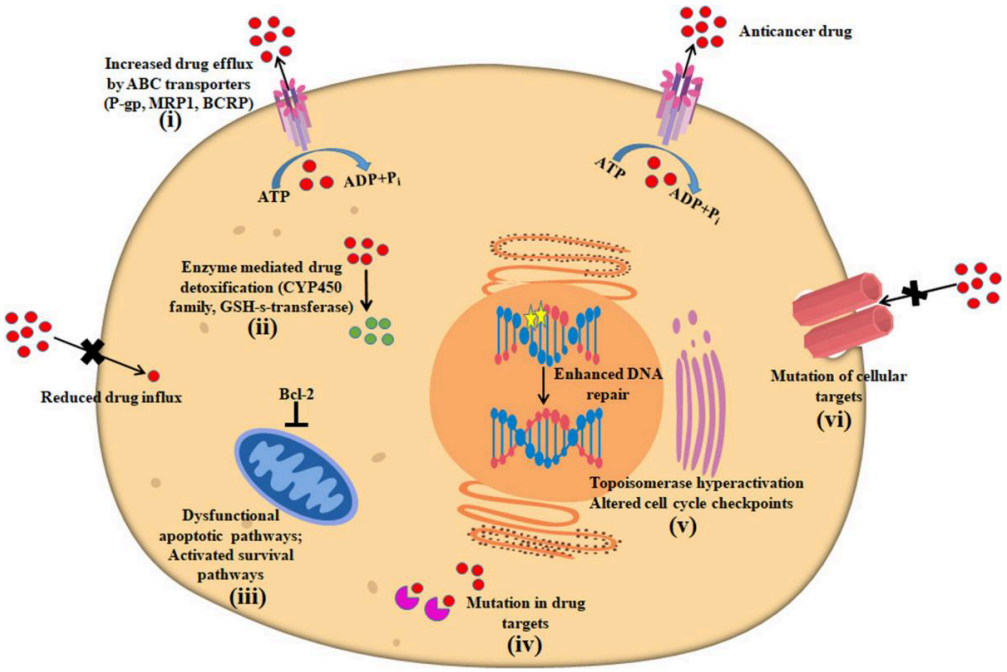
IV. Limitations of Conventional Chemotherapy

Conventional chemotherapeutic agents remain the cornerstone of breast cancer management; however, their clinical application is associated with several drawbacks including:

- Systemic toxicity
- Lack of tumor selectivity

- Multidrug resistance
- Severe adverse effects
- Tumor recurrence
- Metastatic progression

Chemotherapy-induced multidrug resistance primarily occurs through overexpression of ATP-binding cassette transporters, alterations in apoptotic pathways, enhanced DNA repair mechanisms, and activation of survival signaling pathways [13].



Mechanisms contributing to the development of MDR in cancer cells. Various mechanisms such as (i) increased drug efflux by ABC drug transporters, (ii) inactivation of drugs via cellular metabolism and detoxification, (iii) dysfunctional apoptotic pathways, (iv) mutations in drug targets, (v) enhanced DNA repair mechanisms and (vi) mutations in cellular targets play roles in the development of cancer MDR

Precision medicine and targeted therapeutics have improved treatment outcomes; however, the emergence of resistant tumor clones continues to limit long-term efficacy [14]. Therefore, the discovery of structurally novel heterocyclic hybrids capable of targeting multiple oncogenic pathways simultaneously remains an important research priority.

V. Importance of Heterocyclic Scaffolds in Anticancer Drug Discovery

Heterocyclic compounds occupy a central position in medicinal chemistry because of their diverse pharmacological activities and favorable physicochemical properties [15]. Several clinically approved anticancer drugs contain heterocyclic nuclei that facilitate interactions with biological macromolecules such as enzymes, receptors, and nucleic acids.

Chromene derivatives have gained attention due to their broad-spectrum anticancer activity and ability to inhibit tumor growth through multiple mechanisms including apoptosis induction, inhibition of tubulin polymerization, oxidative stress generation, and kinase inhibition [18].

The 1,2,4-oxadiazole scaffold is particularly valuable because it functions as a bioisostere for esters and amides, thereby improving metabolic stability, lipophilicity, and bioavailability. Oxadiazole-containing compounds exhibit diverse biological activities including anticancer, antimicrobial, anti-inflammatory, and kinase inhibitory effects.

The combination of chromene and oxadiazole pharmacophores into hybrid molecules offers synergistic biological activity and improved therapeutic potential.

VI. Microwave-Assisted Green Synthesis

Green chemistry principles emphasize environmentally sustainable chemical processes that minimize hazardous waste, reduce energy consumption, and improve reaction efficiency. Microwave-assisted synthesis has emerged as a powerful green synthetic technique in modern medicinal chemistry.

Advantages of microwave-assisted synthesis include:

- Rapid heating and uniform energy distribution
- Reduced reaction time
- Improved reaction yields
- Cleaner reaction profiles
- Reduced solvent usage
- Enhanced selectivity
- Energy efficiency

Microwave irradiation accelerates molecular collisions and dipolar polarization, resulting in faster reaction kinetics compared with conventional heating methods.

Multicomponent reactions (MCRs) under microwave conditions are particularly useful for synthesizing heterocyclic compounds because they allow rapid assembly of structurally complex molecules in a single synthetic step [16].

VII. Microwave-Assisted Synthesis of Chromene Derivatives

Chromene derivatives are commonly synthesized using one-pot multicomponent reactions involving aldehydes, malononitrile, and phenolic compounds under microwave irradiation [18].

Typical microwave-assisted synthesis involves:

1. Knoevenagel condensation
2. Michael addition
3. Intramolecular cyclization

Microwave-assisted synthesis significantly decreases reaction time from several hours to a few minutes while improving product yield and purity.

Green catalysts commonly employed include:

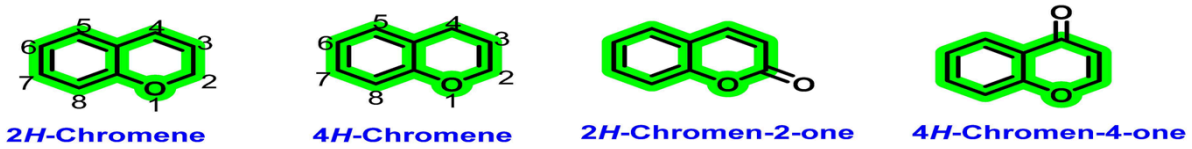
- Ionic liquids
- Metal nanoparticles
- Biocatalysts
- Deep eutectic solvents

- Recyclable heterogeneous catalysts

These environmentally benign methodologies align with sustainable pharmaceutical manufacturing practices.

VIII. Anticancer Potential of Chromene-Based Hybrids

Chromene-based hybrids have demonstrated significant cytotoxic activity against various cancer cell lines including breast cancer, lung cancer, colon cancer, and leukemia.

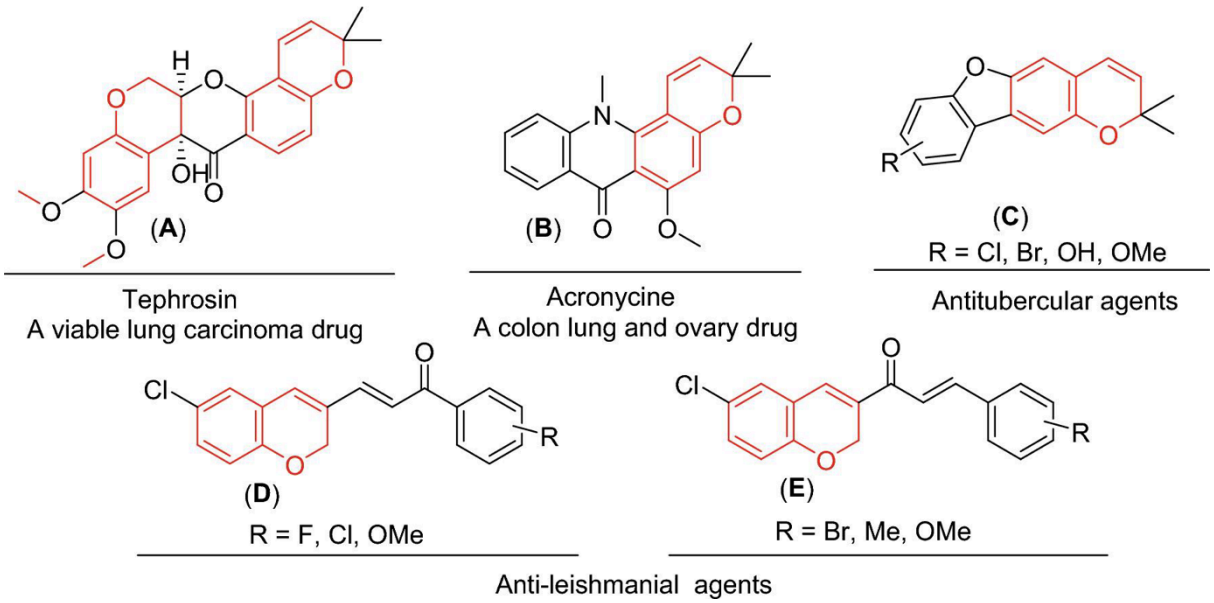


Mechanisms underlying the anticancer activity of chromene derivatives include:

- EGFR inhibition
- Induction of apoptosis
- Cell cycle arrest
- Reactive oxygen species generation
- Antiangiogenic activity
- Inhibition of metastasis

Mostafa et al. synthesized chromene-azo sulfonamide hybrids exhibiting potent anticancer activity with significant EGFR, hCAII, and MMP-2 inhibitory effects [19].

The chromene scaffold also contributes to favorable pharmacokinetic properties and enhanced receptor-binding interactions, making it a privileged platform for anticancer drug development [20].



IX. EGFR as a Therapeutic Target in Breast Cancer

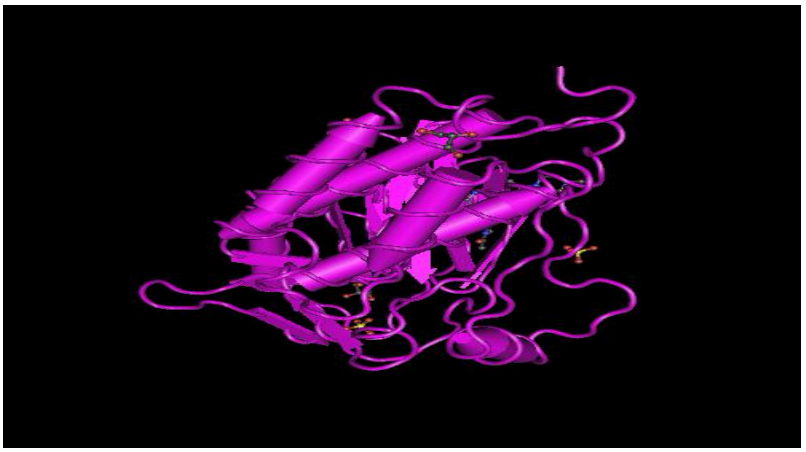
EGFR is a transmembrane receptor tyrosine kinase that regulates cellular proliferation, survival, migration, and angiogenesis. Dysregulated EGFR signaling contributes to breast cancer progression and therapeutic resistance [17].

Upon ligand binding, EGFR undergoes dimerization and autophosphorylation, activating downstream pathways such as:

- PI3K/AKT/mTOR
- RAS/RAF/MEK/ERK
- JAK/STAT signaling

Small-molecule EGFR inhibitors block ATP-binding sites within the tyrosine kinase domain, thereby suppressing tumor growth and inducing apoptosis [17].

Chromene–1,2,4-oxadiazole hybrids have shown promising interactions with EGFR active sites in molecular docking studies, suggesting their potential as targeted breast cancer therapeutics.



Crystal structure of the EGFR kinase domain

X. Structure–Activity Relationship (SAR) of Chromene–1,2,4-Oxadiazole Hybrids

Structure–activity relationship studies indicate that biological activity is strongly influenced by electronic, steric, and lipophilic substitutions on the chromene and oxadiazole rings.

Key SAR observations include:

- Electron-withdrawing groups enhance EGFR inhibitory activity
- Halogen substitutions improve lipophilicity and receptor binding
- Methoxy substitutions enhance cytotoxicity
- Aromatic heterocyclic substitutions improve molecular stability
- Hybridization increases multitarget interactions

Molecular hybridization of chromene and oxadiazole pharmacophores enhances anticancer potency through synergistic modulation of multiple signaling pathways.

XI. Future Perspectives

The future development of chromene–1,2,4-oxadiazole hybrids is expected to involve multidisciplinary approaches integrating medicinal chemistry, computational biology, nanotechnology, and precision oncology.

Important future directions include:

- Artificial intelligence-assisted drug design
- Nanoformulation-based targeted delivery
- Personalized medicine approaches
- Combination therapy strategies
- In vivo pharmacokinetic studies
- Clinical translation and toxicity evaluation

Advanced molecular docking, dynamics simulation, and quantitative structure–activity relationship studies may facilitate the rational optimization of chromene–oxadiazole hybrids with improved therapeutic indices.

XII. Conclusion

Breast cancer continues to represent a major global health challenge despite substantial advances in diagnosis and treatment. Conventional chemotherapeutic approaches are often limited by systemic toxicity, multidrug resistance, and poor selectivity, thereby necessitating the development of novel targeted therapeutics.

Chromene and 1,2,4-oxadiazole scaffolds have emerged as highly promising heterocyclic pharmacophores with significant anticancer potential. Their hybridization offers synergistic biological activity through modulation of EGFR signaling, apoptosis induction, and inhibition of tumor progression pathways.

Microwave-assisted green synthesis provides an efficient, sustainable, and environmentally friendly platform for the rapid generation of structurally diverse chromene–1,2,4-oxadiazole hybrids with improved yields and reduced environmental impact.

Overall, chromene–1,2,4-oxadiazole hybrids represent a promising class of multifunctional anticancer agents for breast cancer therapy. Continued research integrating green chemistry, molecular docking, nanotechnology, and precision medicine may accelerate their transition from laboratory research to clinical application.

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