REVIEW PAPER

Modulation of Oxidative Stress and Apoptotic Pathway by Embelin and Curcumin Analogues in Cancer

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ABSTRACT

Cancer is a primary cause of morbidity and mortality globally, defined by uncontrolled cellular proliferation, genomic instability, and the evasion of programmed cell death. Although there have been advancements in chemotherapy and radiotherapy, these modalities frequently exhibit limited selectivity, significant toxicity, and the emergence of resistance. As a result, naturally derived bioactive compounds have garnered significant interest due to their multitargeted mechanisms and enhanced safety profiles. Embelin, a benzoquinone derivative from Embelia ribes, and Curcumin, a polyphenolic compound from Curcuma longa, demonstrate significant potential in modulating oxidative stress and apoptotic pathways, which are critical processes in cancer pathophysiology. This review examines the effects of Embelin and Curcumin analogues on redox homeostasis and the regulation of apoptosis in cancer models. Literatures were sourced from PubMed, ScienceDirect, Scopus, and MDPI utilising pertinent keywords, with inclusion criteria centred on oxidative stress modulation and the activation of apoptotic pathways. Research demonstrates that both compounds exhibit dual redox behaviour, functioning as antioxidants in normal cells while creating pro-oxidant conditions in tumour cells to initiate apoptosis. Embelin functions by inhibiting the X-linked inhibitor of apoptosis protein (XIAP), which leads to the activation of caspase-9 and caspase-3. In contrast, Curcumin modulates both intrinsic (mitochondrial) and extrinsic (death receptor) pathways by influencing reactive oxygen species (ROS), NF-κB, and Bcl-2 family proteins. Their combination exhibits synergistic effects by augmenting ROS-mediated apoptosis and inhibiting tumour survival signalling. The findings collectively underscore the potential of Embelin and Curcumin analogues as promising candidates for next-generation anticancer therapeutics. Future research should focus on nanoformulations strategies and clinical validation to address the challenges of solubility and bioavailability.

Keywords: Embelin, Curcumin analogues, Oxidative stress, Apoptosis, Cancer, ROS modulation.

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INTRODUCTION

Cancer remains a major global challenge due to its high incidence and mortality rates. Every year, millions of new cancer cases are identified. As a part of the global effect to eradicate cancer, numerous nations have already started investing their efforts to achieve goal through various national and international programs [1,2]. Depending on the cancer type and grade as well as the situations of patients, physicians prescribe one or more modalities for tumour control. Some cancers may not be curable. However, most cancers can be treated [2,3]. Targeting oxidative stress and apoptotic pathway, opens new possibilities for more effective and synergistic cancer treatment. Cancer refers to a group of disease that arises from mutated cells that have acquired the capacity to proliferate indefinitely and evade apoptosis, which eventually leads to a tumour formation and subsequently invasion to surrounding tissues. Current cancer treatment options include surgical intervention, chemotherapy and radiation therapy or a combination of these options [4]. Current anti-cancer drugs possess various limitations, including adverse effects such as, immunosuppression, cardiotoxicity, significant hair loss, mucositis, myelosuppression, and systemic toxicity due to non-specific drug distribution. Extensive studies are focused on plant-based molecules to develop effective cancer medicine [1,5].

Redox homeostasis plays a critical role in determining cancer cell fate, as moderate levels of Reactive Oxygen Species (ROS) support tumour growth, angiogenesis, and metastasis, whereas excessive oxidative stress triggers irreversible apoptotic signalling. Malignant cells exhibit altered mitochondrial function, aberrant redox signalling, and enhanced resistance to apoptosis, creating a therapeutic vulnerability that can be exploited. The intimate connection between oxidative stress and apoptosis is mediated through key regulators such as mitochondrial membrane permeabilization, death receptor activation, and caspase cascades, positioning redox

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modulation as a central target in anticancer drug development [6].

Natural products have attracted the attention of several research scientists for the development of antitumour drugs, due to their proven efficacy and safety. Natural products play an important role in the discovery of lead compounds, and several natural products have been developed and used in clinical practice due to their potent antitumour properties, such as vincristine, camptothecin and paclitaxel. Thus, natural products may represent excellent sources of novel antitumour agents, and a number of them must be further characterized [7].

Embelin [**2,5-dihydroxy-3-undecylcyclohexa-2,5-diene-1,4-dione]** , a benzoquinone compound derived from *Embelia ribes* (see Figure 1 & Figure 2) and Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] , a polyphenolic compound derived from *Curcuma longa* (see Figure 3 & Figure 4) are the most important natural compounds which possess multiple antitumour properties [8–11]. Both compounds influence various molecular pathways central to cell survival and death, making them promising candidates for cancer therapy [7,11,12].

Despite promising anticancer properties, the clinical translation of embelin and curcumin is limited by challenges such as poor solubility, low bioavailability, and rapid metabolic degradation. To overcome these limitations, extensive efforts have been devoted to the synthesis and evaluation of embelin and curcumin analogues with improved pharmacokinetic and pharmacodynamic profiles. These analogues demonstrate enhanced efficacy through precise targeting of oxidative stress–responsive pathways and apoptosis-regulatory proteins, including X-linked Inhibitor of Apoptosis Protein (XIAP), B-cell lymphoma 2 (BCL-2) family members, and caspases. Understanding the molecular mechanisms underlying the redox-apoptotic modulation by these analogues may facilitate the development of more effective, selective, and safer anticancer therapeutics.

Embelin overcomes its protective effect of XIAP, which is potent inhibitor of apoptosis and remains overactive in cancer cells [4,13]. The anti-apoptotic properties of XIAP are attributed to the inhibition and proteasome degradation of caspases and other signalling pathways. Really Interesting New Gene (RING) domain of XIAP bears presence of a carboxylic acid (COOH) moiety, which is considered a ubiquitin conjugation and proteasomal degradation site, whereas, Baculovirus IAP Repeat (BIR3) domain acts on initiator gene caspase-9 and Baculovirus IAP Repeat (BIR2) domain acts on effector gene caspase-3 and caspase-7, thereby attributing towards anticaspase activity . On the other hand Curcumin act by controlling oxidative stress and reduces harmful ROS level [14]. Curcumin influences both the extrinsic and intrinsic pathways. Together curcumin and embelin exert synergistic anticancer effects through regulations of oxidative stress and apoptotic pathways making it a therapeutic strategy in cancer management [15,16].

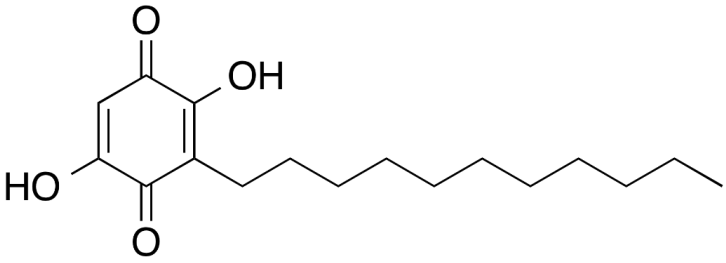

Figure 1: - Molecular Structure of Embelin

Figure 2: - *Embelia ribes* [17]

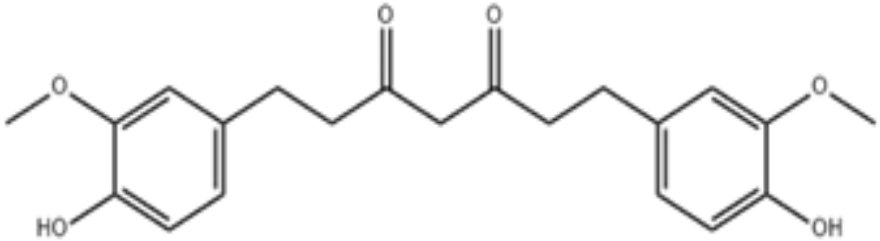

Figure 3: - Molecular Structure of Curcumin

Figure 4: - *Curcuma longa* [18]

OXIDATIVE STRESS MODULATION

Oxidative stress provides a pivotal role in cancer initiation, progression, and resistance to chemotherapeutic agents. It also represents a major hallmark in cancer progression and drug resistance. It arises from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defence mechanism that to neutralize them. ROS naturally produced during aerobic metabolism and mitochondrial oxidative phosphorylation. ROS can disrupt cellular redox homeostasis and trigger apoptotic cell death, highlighting the dual nature of oxidative stress in cancer biology. In cancer biology, oxidative stress plays a paradoxical role it can both promote and suppress tumourigenesis. Modulation of oxidative stress has emerged as a promising therapeutic strategy to overcome multidrug resistance (MDR) and improve cancer prognosis. Several natural bioactive compounds, including curcumin, have demonstrated the ability to regulate intracellular ROS levels and influence redox-sensitive signalling pathways [19,20]. The modulation of oxidative stress involves intricate regulation of cellular antioxidant networks. Key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), act in concert with non-enzymatic antioxidants such as glutathione, vitamins C and E, and flavonoids to maintain redox equilibrium [21].

i) Embelin

Embelin, a bioactive compound obtained from *Embelia ribes*, that provide antioxidant properties that help balance oxidative stress in the body. It works both directly or indirectly to decrease or reduce the harmful effects of ROS, especially superoxide radicals, which can harm cells and tissues [22–24]. By neutralizing these free radicals and inhibiting lipid peroxidation, embelin help protects cell membranes and essential cellular components from oxidative damage. Besides its direct antioxidant effects, embelin also enhances the body's natural defense mechanism[17,25]. It activates the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway, which increase or boosts the generation of vital antioxidant enzymes such as superoxide dismutase (SOD) catalase and glutathione. These enzymes are crucial for maintaining cellular redox balance and protective against oxidative harm. Scientific research has demonstrated that embelin offers strong cytoprotective effects in cellular models and reduces oxidative stress in various pathological conditions, such as obesity and neuroinflammation. Overall Embelin shows greater promise for the prevention and treatment of oxidative stress related metabolic and inflammatory disorders [17,26,27].

ii) Curcumin

Curcumin causes oxidative stress in tumour cells and leads to cell death. Curcumin is classically known as antioxidant as it can activate the Nrf2 antioxidant response element pathway, upregulating antioxidant enzymes and suppressing reactive oxygen species (ROS) in non-tumour and non-stressed contexts. Paradoxically, in tumour cells or under certain conditions, curcumin can induce oxidative stress (increase ROS) to damage cancer cells and trigger cell death [28]. Mechanism by which curcumin induces oxidative stress in tumour cells are mitochondrial damage & ROS overproduction, activation of apoptosis, autophagy induction via ROS, ferroptosis, pyroptosis (inflammatory cell death). Curcumin can synergize with chemotherapy drugs by increasing ROS in tumour cells, sensitizing them to apoptosis while potentially protecting normal cells via its antioxidant role. At lower dose or in normal (non-transformed) cells, curcumin may upregulate antioxidant defense; at higher dose, or in tumour cells with compromised redox buffering, curcumin may suppress antioxidant enzyme and drive ROS [7,29].

APOPTOTIC PATHWAY MODULATION

Embelin and curcumin are natural compound that modulate apoptotic pathways in cancer cells through various mechanisms often target some pathways at once.

Both compounds show promising anticancer effects by including apoptosis [30–32]. Embelin and curcumin which is known to be a potent small molecule inhibitor of the XIAP that abrogates binding of XIAP to procaspase –9. It acts as a potent inhibitor of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) [33–35]. Apoptosis plays a major role in controlling cellular integrity and is strictly regulated.

Two main distinct apoptotic pathways have been developed, the intrinsic and extrinsic pathways [36–38]. In the apoptosis pathways, Inhibitor of Apoptosis (IAPs) are important signalling components that negatively regulate apoptotic caspase 3/7, therefore prevent cells from apoptosis[30,32,39]

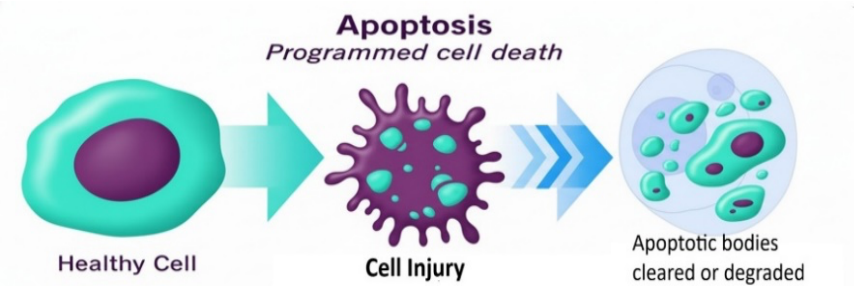

Figure 5: Apoptosis.

Intrinsic (mitochondrial) pathway activation

Embelin and curcumin alters the balance of anti-apoptotic and pro apoptotic proteins B-cell lymphoma 2, B-cell lymphoma-extra-large (Bcl-2, Bcl-xl) and enhancing the expression of pro apoptotic proteins Bcl-2-associated X protein (Bax) which leads to the permeabilization of mitochondrial membrane and release cytochrome C. The release of cytochrome C triggers the activation of initiator caspase-9 and subsequently the executioner caspases-3 and caspase-7 leading to cell death [40–42]. In the intrinsic pathway, cellular stress signals promote mitochondrial outer membrane permeabilization (MOMP), which is regulated by BCL-2 family proteins such as BAX and Bcl-2 antagonists/killer (BAK). MOMP results in the release of key pro-apoptotic factors, including cytochrome c and Second mitochondria derived activator of caspases (SMAC), into the cytosol. Cytochrome C binds to Apoptotic Protease Activating Factor 1 (APAF-1) in the presence of Deoxyadenosine triphosphate (dATP), leading to the formation of the apoptosome, a multi-protein complex that recruits and activates procaspase-9. Activated caspase-9 subsequently triggers the activation of executioner caspases caspase-3, -6, and -7, driving the apoptotic process. SMAC further amplifies apoptosis by antagonizing XIAP, an inhibitor of caspases, thereby relieving caspase suppression.

Extrinsic (death receptor) pathway activation

Embelin can restore or enhance sensitivity to Tumour Necrosis Factor (TNF) related apoptosis including Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) ligand which is achieved by XIAP inhibition and downregulating proteins like Cellular FLICE-like inhibitory protein (cFLIP). In some cases, it increases the Death Receptor 4 & 5 (DR4 & DR5) receptor which make the cell more susceptible to TRAIL mediated apoptosis [42–44].The death effector domain (DED) is a protein interaction that enables recruitment of initiator caspases. Upon ligand binding, death receptors assemble the death-inducing signalling complex (DISC). DISC activates initiator caspases. These initiator caspases then activate executioner caspases. Embelin can also induce apoptosis by inhibiting pro survival signalling pathways like NF-κB, PI3K/Akt (Phosphatidylinositol 3-kinase/Protein kinase B) , and Signal Transducer and Activator of Transcription 3 (STAT3). Curcumin can activate the extrinsic pathway by increasing Fass Ligand (FasL) expression and TRAIL-induced apoptosis by sensitizing cells. Curcumin is a potent inhibitor of the NF-κB it regulates anti apoptotic protein and promote cancer cell by blocking NF-κB, it supress inflammation and promote apoptosis [35]. Both Embelin and Curcumin triggers caspase-9 which further activates caspase-3 & caspase-7 leading to cell death (see Table 1). On the other hand, Curcumin supress PI3K/AKt pro-survival pathway by inhibiting Akt phosphorylation leads to downstream signal and thereby enhancing apoptosis. STAT3 activation is common in many cancers [45–47]. Curcumin inhibits STAT3 signalling leading to decrease of STAT3 - regulated gene involves in proliferation. Curcumin can increase intracellular reactive oxygen species (ROS) which cause Deoxyribonucleic acid (DNA) damage and activate pathways like c-Jun N-terminal kinase (JNK) and P38 Mitogen-Activated Protein Kinase (P38 MAPK) that trigger apoptosis [48] and these mechanisms are required for effective apoptosis in certain cells which undergo extrinsic apoptosis independently of intrinsic pathway induction (see Figure 6).

Table 1: Effects of Embelin and Curcumin Analogues on Key Signalling Pathways and Oxidative Stress-Induced Apoptosis

Compound	Key targets & pathway	Oxidative stress &	References

		Apoptotic Effect	
Embelin	XIAP/NF-κB/PI3K/AKT	• Increase ROS via mitochondrial dysfunction. • Acts both Intrinsically & Extrinsically	9,20,31
Curcumin	Nrf2/STAT3/MAPK	• Induces ROS burst in cancer cell. • Acts both Intrinsically & Extrinsically	21,25,31

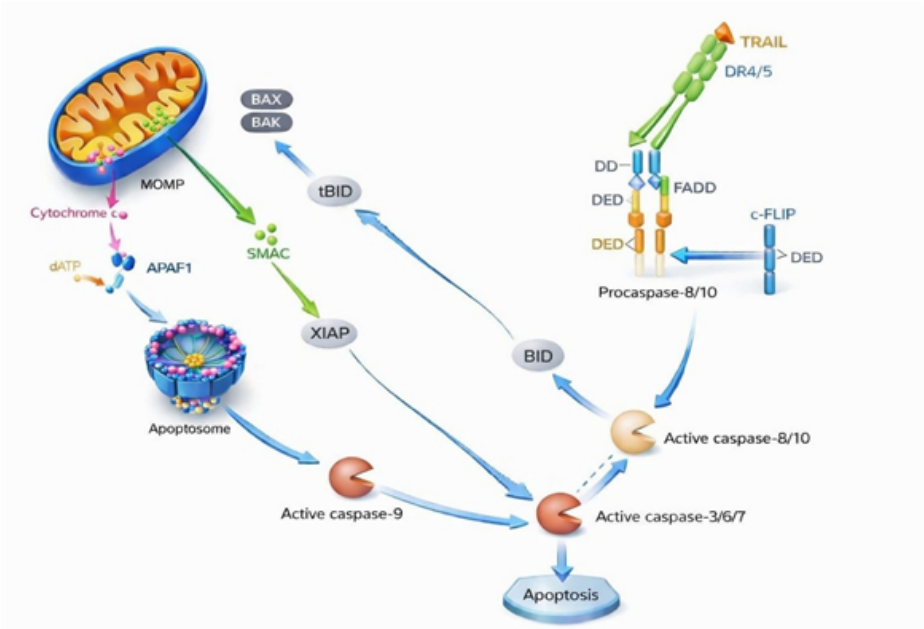

Figure 6: Molecular Pathways of Apoptosis – Intrinsic (Mitochondrial) and Extrinsic (Death Receptor–Mediated) Signalling Cascades. In the intrinsic pathway, cellular stress signals promote mitochondrial outer membrane permeabilization (MOMP), which is regulated by BCL-2 family proteins such as BAX and BAK. MOMP results in the release of key pro-apoptotic factors, including cytochrome c and SMAC, into the cytosol. Cytochrome C binds to APAF-1 in the presence of dATP, leading to the formation of the apoptosome, a multi-protein complex that recruits and activates procaspase-9. Activated caspase-9 subsequently triggers the activation of executioner caspases caspase-3, -6, and -7, driving the apoptotic process. SMAC further amplifies apoptosis by antagonizing XIAP, an inhibitor of caspases, thereby relieving caspase suppression. The extrinsic pathway is initiated by the binding of death ligands such as TRAIL to death receptors DR4/DR5 on the cell surface. This interaction promotes the recruitment of adaptor proteins containing death domains (DD) and death effector domains (DED), including Fass-Associated protein with Death Domain (FADD), leading to the formation of the death-inducing signalling complex (DISC). Within the DISC, procaspase-8 and -10 are activated. The activation of these initiator

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Table 2: Therapeutic Targets and Molecular Modulation in Cancer Progression

Molecular category	Specific targets	Modulation type	Impact on cancer progression	References
IAPs	XIAP	Downregulation	Reverse resistance to chemotherapy; activates caspase	39
Pro-Apoptotic	Bax, Bak	Upregulation	Induces Mitochondrial Outer Membrane Permeabilization	16
Anti-Apoptotic	Bcl-2, Bcl-xL	Downregulation	Lowers the threshold for cell death signals	49
Redox Enzymes	SOD, Catalase, GSH (Reduced Glutathione)	Inhibition	Increase intracellular ROS to toxic levels in tumour cells	5

Transcription Factors	NF-κB, STAT3	Inhibition	Supresses pro-survival genes and inflammatory cytokines	[27]

SYNERGISTIC POTENTIAL

Synergistic potential describes the likelihood or capacity of two or more drugs, treatments, or substances to produce a combined effect that exceeds the sum of each agent's individual effects when used alone [50]. This property is investigated in preclinical and clinical studies when exploring new treatment regimens or optimizing existing ones [51].

The synergistic effect and dose effect relationship of embelin was determined by median effect principle. Combinational therapies refer to administering two or more medications simultaneously to address different elements of the disease's pathophysiology. This technique can potentially change the treatment of various disorders by improving medication delivery, minimizing side effects and targeting several disease pathways simultaneously compared to single drug deliveries with nanoformulations. In a recently reported study, Donepezil hydrochloride (DPL) and embelin loaded Nanostructured Lipid Carrier (NLCs) to get the highest possible drug loading, provide safer administration [17,52]. Curcumin shows strong synergistic effect when combined with other anticancer agents and therapies, significantly enhancing their effectiveness against multiple types of cancer through diverse molecular pathways. This synergy enables lower drug doses, reduces side effects, and helps overcome drug resistance in cancer treatment. Curcumin enhances apoptosis, inhibits proliferation, and affects multiple signalling pathways including PI3K/AKT, STAT3, NF-κB and Wingless-related intrgration site (Wnt)/ β-catenin, which are pivotal in tumour progression and resistance. When combined with chemotherapy agents such as cisplatin, doxorubicin, paclitaxel or 5-fluorouracil, curcumin boosts their anti-cancer activity and efficacy [53]. Curcumin enhances the effect of conventional cancer therapies, delivering improved outcomes in combination regimens [3,54]. Novel nanoparticle liposome, and phytosomal formulations of Curcumin dramatically improve its pharmacokinetics, cellular uptake, and anti-tumour action. Such advances now allow co-delivery with other chemotherapeutics for stronger and more targeted glioblastoma, breast and pancreatic cancers [55,56].

FUTURE PERSPECTIVE

Future research on the modulation of oxidative stress and apoptotic pathways by embelin and curcumin analogues in cancer therapy holds promising potential. Both compounds have shown notable antioxidant and pro-apoptotic effects, yet their clinical translation remains limited due to issues such as low bioavailability, metabolic instability, and poor target specificity. The development of novel analogues and nanoformulations could enhance their pharmacokinetic properties and therapeutic efficacy. Moreover, combining embelin and curcumin analogues with conventional chemotherapeutic agents or immunotherapies may offer synergistic effects, reduce toxicity while improve cancer cell selectivity. Advanced molecular docking, omics-based profiling, and in vivo studies are needed to clarify their precise molecular interactions with oxidative and apoptotic signalling networks. Future work should also focus on understanding patient-specific responses to these agents, paving the way for personalized antioxidant-based cancer therapies.

The future of cancer therapy lies in harnessing nature-inspired molecules like embelin and curcumin analogues that can precisely modulate oxidative stress and apoptotic signalling. Advancements in nanotechnology, molecular docking, and structure–activity optimization present exciting opportunities to overcome their limitations of bioavailability and target specificity. Integrating these compounds into smart drug delivery systems or hybrid formulations could transform them into next-generation anticancer agents with enhanced cellular selectivity and minimal toxicity. Furthermore, exploring their synergistic potential with immunotherapy and redox-modulating drugs may unveil new therapeutic pathways against resistant cancer types. Additionally, exploring synergistic interactions between these analogues and existing chemotherapeutic agents could offer new combination strategies for improved efficacy and reduced resistance. Comprehensive molecular and pharmacodynamic studies, coupled with well-designed clinical trials, are essential to fully harness the therapeutic potential of embelin and curcumin analogues in the management of diverse cancer types.

Future research should focus on developing advanced drug delivery systems, such as nanoparticles or liposomal formulations, to enhance their systemic retention and tumour-specific accumulation. Additionally, exploring synergistic interactions between these analogues and existing chemotherapeutic agents could offer new combination strategies for improved efficacy and reduced resistance. Comprehensive molecular and pharmacodynamic studies, coupled with well-designed clinical trials, are essential to fully harness the therapeutic potential of embelin and curcumin analogues in the management of diverse cancer types. Future research should focus on developing advanced drug delivery systems, such as nanoparticles or liposomal formulations, to enhance their systemic retention and tumour-specific accumulation.

CONCLUSION

Embelin and Curcumin analogues exhibit significant anticancer potential through their ability to modulate oxidative stress and apoptotic pathways. By reducing excessive reactive oxygen species and re-establishing cellular oxidative balance, these bioactive substances serve as important redox regulators, preventing damage to DNA and mitochondria. By modifying important molecular mediators like caspases, tumour protein p53, Bcl-2 family proteins, and NF-κB, they simultaneously cause apoptosis, which promotes the death of cancer cells while reducing harm to healthy tissues. These analogues' pharmacokinetic

stability, target affinity, and therapeutic efficacy have all been further improved by structural modifications, highlighting their significance as new anticancer drugs. Embelin and curcumin analogues combined dual modulation of oxidative and apoptotic signalling suggests that they could be incorporated into next-generation cancer treatments.

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