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Overcoming Curcumin's Limitations: Synthetic Derivatives in Diabetes and Cancer Management

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ABSTRACT

Non-communicable diseases (NCDs), such as diabetes and cancer, are chronic medical conditions characterised by their persistent nature and gradual progression. They pose a significant challenge to global public health due to their widespread impact and increasing prevalence worldwide. According to the 2021 International Diabetes Federation atlas reports, 10.5% of adults worldwide currently live with diabetes, a figure projected to reach 783 million by 2045. Furthermore, cancer is one of the world's top causes of death, as reported by the WHO. Although synthetic drugs are widely used to manage these diseases, they often come with adverse side effects such as suppression of blood cell production, inflammation of mucous membranes, hair loss, and nausea. Curcumin, an active compound found in turmeric, has attracted interest due to its therapeutic potential in treating both diabetes and cancer, largely owing to its favourable safety profile, as evidenced by preclinical and clinical data. Nevertheless, poor bioavailability, rapid metabolism, and low stability in living systems have limited its clinical application. To address these limitations, recent research has focused on developing synthetic curcumin derivatives with improved pharmacokinetic properties. This review examines the antidiabetic and anticancer potentials of these derivatives, emphasising research data from both in vivo and in vitro studies. The paper also highlights how structural modifications significantly enhance their biological activity and provides a comparative mechanistic discussion linking diabetes and cancer at the molecular level, and translational gaps that define future research directions. This dual perspective in mechanisms distinguishes the present review from earlier works that examined curcumin's therapeutic potential in isolation within diabetes or cancer frameworks.

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 5-FU, 5-fluorouracil; Akt, protein kinase B; AR, androgen receptor; BAD, B-cell lymphoma (Bcl) 2-associated death promoter; BDMC, bisdemethoxycurcumin; BIM, B-cell lymphoma (Bcl) 2-like protein 11; Caco-2, human colon carcinoma cell line; CAT, catalase; CRPC, castration-resistant prostate cancer; Cur-5-FU, curcumin–5-fluorouracil hybrid; DMSO, dimethyl sulfoxide; DPP-IV, dipeptidyl peptidase-IV; FABP-4, fatty acid-binding protein 4; FFAs, free fatty acids; G2/M, cell-cycle G2/M phase; GLUT-4, glucose transporter Type 4; HeLa, human cervical cancer cell line; HepG2, human hepatocellular carcinoma cell line; HK-2, human kidney proximal tubule epithelial cell line; HO-1, heme oxygenase-1; HT-29, human colon adenocarcinoma cell line; IC_{50}, half-maximal inhibitory concentration; IGF-1, insulin-like growth factor 1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IRS-1, IRS-2, insulin receptor substrate-1 and −2; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; LO-2, normal human liver cell line; MCF-7, human breast cancer cell line; MDM2, murine double-minute 2 protein; mTOR, mammalian target of rapamycin; NCD, novel water-soluble curcumin derivative; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; OGTT, oral glucose tolerance test; p53, tumour suppressor protein p53; PF-915275, selective 11β-HSD1 inhibitor used as comparator compound; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor-gamma; RNS, reactive nitrogen species; ROS, reactive oxygen species; SI, selectivity index; SOD, superoxide dismutase; SREBP1c, sterol regulatory element-binding protein 1c; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TIMP-2, tissue inhibitor of metalloproteinases-2; TNF-α, tumour necrosis factor-alpha; TRAMP, TRAMP-C1, transgenic adenocarcinoma of the mouse prostate model/derived cell line; TrxR, thioredoxin reductase; TS, thymidylate synthase; VEGF, vascular endothelial growth factor.

1 | Introduction

Diabetes mellitus and cancer are among the leading causes of global morbidity and mortality, both characterised by complex metabolic and molecular dysregulation. Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycaemia resulting from insulin deficiency, insulin resistance, or a combination of both [1–3]. Globally, an estimated 10.5% of adults aged 20–79 live with diabetes, with nearly half undiagnosed, and this number is projected to rise to 783 million by 2045 [1]. Insulin, secreted by pancreatic β-cells, is essential for glucose uptake and energy production; when its secretion or action is impaired, glucose accumulates in the bloodstream, leading to systemic complications such as neuropathy, nephropathy, and cardiovascular disease [4]. Diabetes mellitus encompasses several types, including Type 1, Type 2, and gestational diabetes. Type 2 diabetes, the most prevalent form, is characterised by insulin resistance and progressive β-cell dysfunction [5]. Current pharmacological options, including biguanides (e.g., metformin), sulfonylureas, thiazolidinediones, and insulin analogues ameliorate hyperglycaemia but are limited by adverse effects, declining efficacy over time, and inability to fully restore β-cell function [6].

Cancer, on the other hand, remains a leading cause of global mortality, accounting for approximately 20 million new diagnoses and 9.7 million deaths in 2022 [7]. It is characterised by uncontrolled cell proliferation and metastasis resulting from genetic mutations, dysregulated signalling pathways, and impaired cell death mechanisms [8]. Typically, cells in the human body replicate through cell division to produce new cells according to the body's requirements. When cells become old or sustain injury, they die, and new cells emerge in their place. At times, this highly controlled process malfunctions, and abnormal or impaired cells proliferate inappropriately. These cells have the potential to create masses of tissue called tumours, which may either be classified as malignant (cancerous) or benign (non-cancerous). While malignant or cancerous tumours tend to spread across the body, benign or non-cancerous tumours do not [8]. Also, benign tumours typically do not regrow once removed, while malignant tumours may have the potential to regrow. Various cancer types exist, but lung cancer remains the most prevalent, constituting 12.4% of global cases, followed by breast (11.6%), colorectal (9.6%), prostate (7.3%), and stomach (4.9%) cancers [7]. Cancer-associated deaths are also predominantly attributed to lung, colorectal, liver, and breast cancers [7]. At the molecular level, cancer progression involves deregulation of critical pathways such as PI3K/Akt/mTOR, MAPK, and NF-κB, which mediate cell growth, proliferation, and survival [8].

Increasing evidence indicates that diabetes and cancer share overlapping pathophysiological mechanisms, particularly oxidative stress, inflammatory cytokine activation, and altered insulin/IGF-1 signalling [9–11]. Hyperinsulinaemia and elevated IGF-1 in diabetes can enhance mitogenic and anti-apoptotic signalling, thereby promoting tumorigenesis. Conversely, cancer-associated metabolic reprogramming, including enhanced glycolysis and mitochondrial dysfunction, can aggravate insulin resistance. These shared mechanisms underscore the need for therapeutic agents capable of modulating oxidative, inflammatory, and metabolic pathways simultaneously.

Turmeric (*Curcuma Longa*), a perennial herb of the *Zingiberaceae* family, has long been used in traditional medicine across South Africa, Nigeria, India, China, and Southeast Asia for both culinary and therapeutic purposes [12, 13]. Its bioactive component, curcumin (IUPAC: (1E,6E)−1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione; Figure 1), is one of three major phenolic constituents, collectively known as curcuminoids. The other two are demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) [14]. Several studies have investigated the molecular mechanisms through which curcumin exerts therapeutic effects in disease conditions, including diabetes [15–17], neurological disorders [18–20], and osteoarthritis [21–23] (Figure 1). Additionally, the compound has been evaluated in multiple clinical trials [24–26]. Curcumin exhibits potent antioxidant properties, comparable to conventional antioxidants such as vitamins C and E [14]. Additionally, it has been shown to regulate cholesterol metabolism by reducing cholesterol absorption in the small intestine, thereby lowering circulating lipid levels [27]. More importantly, curcumin has demonstrated broad-spectrum anticancer properties through its inhibition of several cancer cell types [28], including gastric cancer [29], B-cell tumours, T-cell leukaemia, and colon carcinoma [30]. In vivo, it suppresses the progression of colon, liver, pancreatic, skin, and prostate cancers [31–35]. Compared to many conventional chemotherapeutic agents, curcumin has demonstrated a more favourable toxicity profile in preclinical models [36].

Despite the remarkably non-toxic and proven bioactivities of curcumin, a significant drawback is its excessive hydrophobic nature, which leads to poor absorption across the intestinal barrier, posing an obstacle to its medical use [14]. Structural analyses suggest that the presence of the β-diketone moiety contributes to curcumin's metabolic instability and suboptimal pharmacokinetic profile [37]. Pharmacokinetic studies report extremely low plasma concentrations following oral administration of curcumin due to rapid first-pass metabolism, restricted systemic distribution, and accelerated clearance [38–41]. These limitations have spurred efforts to enhance curcumin's bioavailability and therapeutic efficacy through structural modifications and novel delivery strategies. These modifications enhance solubility, metabolic stability, and target selectivity, thereby broadening curcumin's therapeutic potential for complex diseases.

While previous reviews have primarily focused on natural curcumin, this review highlights recent advances in synthetic derivatives of curcumin with therapeutic potential against diabetes mellitus and cancer. This review not only compiles recent findings on curcumin derivatives but also provides a comparative mechanistic discussion linking diabetes mellitus and cancer at the molecular level. By doing so, it aims to establish a more integrated understanding of curcumin derivatives as multifunctional therapeutic agents. Furthermore, this review highlights how structural modifications and novel formulations of curcumin derivatives can overcome pharmacokinetic barriers, thereby enhancing their bioavailability and therapeutic efficacy. It also highlights their translational challenges and limitations,

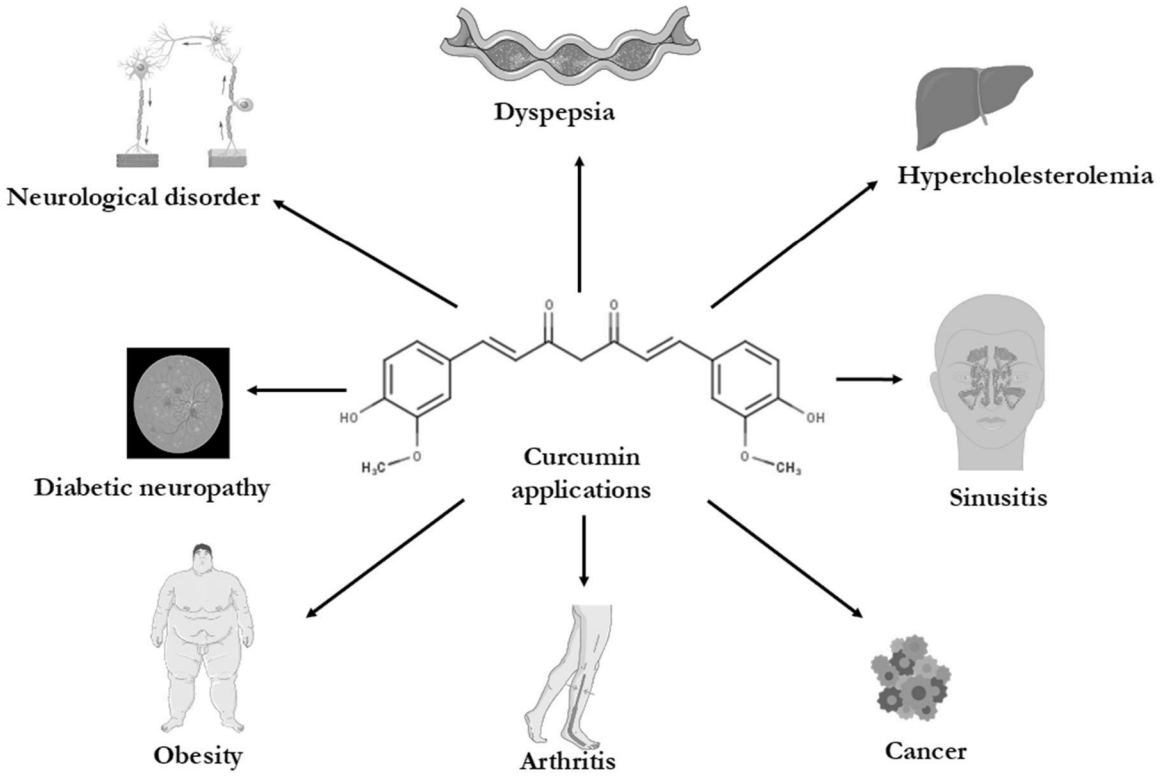

FIGURE 1 | Curcumin structure and therapeutic applications.

while providing future perspectives on their potential translational applications.

2 | Method

Various scientific databases, such as PubMed, Scopus, Google Scholar, and Web of Science were used to gather literature for this review, using keywords such as "curcumin's biological activities", "curcumin derivatives", "curcumin derivatives and diabetes", "curcumin derivatives and cancer", "antidiabetic properties of curcumin derivatives", "anticancer properties of curcumin derivatives", and "interlinked molecular mechanism between diabetes and cancer". This review utilised more than 50 research materials that were chosen during the search process.

3 | Antidiabetic Properties of Curcumin Derivatives

Numerous synthetic derivatives of curcumin have been extensively investigated for their potential in managing diabetes mellitus and its associated complications. A comprehensive summary of these studies is presented in Table 1. Reported mechanisms underlying their antidiabetic effects include the inhibition of carbohydrate-metabolising enzymes, modulation of insulin signalling pathways, suppression of gluconeogenesis, and enhancement of pancreatic β-cell function [41].

Das et al. [42] synthesised 10 curcumin analogues and screened their hypoglycaemic activity using the glucose oxidase-peroxidase assay, in vitro. Among these, 1,7-bis(3,4-dimethoxyphenyl)-hepta-1,6-diene-3,5-dione (**1**) and 1,5-bis(4-hydroxy-3-methoxyphenyl)-penta-1,4-dien-3-one (**2**) (Figure 2) exhibited the most potent glucose-lowering effects, showing a concentration-dependent reduction in glucose levels. At 20 mg/dL glucose, Compounds **1** and **2** achieved 93.35% and 76.65% glucose reduction, respectively, while at 100 mg/dL, the reductions were 50.97% and 27.82%. The authors attributed this potency to the electron-donating capacity of the enolic β-diketone moiety, which can stabilise radicals similarly to phenolic antioxidants, thereby modulating glucose oxidation.

In vivo evaluation further revealed that oral administration of Compound **1** (100 μg/kg) reduced fasting blood glucose by 44.45% within 2 h, comparable to the 52.53% decrease produced by glipizide, a standard antidiabetic drug [42]. The comparable response suggests that methoxylation of the phenolic groups may increase membrane permeability and support insulin secretagogue-like activity, possibly through stimulation of stored insulin release from pancreatic β-cells. In contrast, Compound **2**, though effective in vitro, showed weaker in vivo activity, underscoring the influence of chain length and conjugation on bioavailability and pharmacodynamic stability.

Zhao et al. [43] developed another synthetic curcumin derivative, (2E,6E)−2,6-bis(2-(trifluoromethyl)benzylidene)-cyclohexanone (LG13, **3**) (Figure 2), and evaluated its efficacy in a Type 2 diabetic mouse model induced with a low-dose streptozotocin-high-fat-diet combination. Oral administration of 5 mg/kg of Compound **3** for 6 weeks produced a 53.8% reduction in fasting glucose relative to diabetic controls, a response sustained throughout treatment and more pronounced than that of the standard antidiabetic drugs pioglitazone and PF-915275. Molecular analyses demonstrated that Compound **3** restored phosphorylation of Akt and prevented its deactivation, thereby

TABLE 1 | Summary of antidiabetic properties of curcumin derivatives.

Curcumin derivative	Study type	Dosage	Treatment duration	Mechanism	Reference
1,7-bis(3,4-dimethoxyphenyl) hepta-1,6-diene-3,5-dione, **1**	In vivo	100 μg/kg	2 h	↓ Blood glucose	[42]
	In vitro	500 μM	N/A	↓ Glucose concentration	
1,5-bis(4-hydroxy-3-methoxyphenyl) penta-1,4-dien-3-one, **2**	In vitro	500 μM	N/A	↓ Glucose concentration	[42]
(2E,6E)−2,6-bis(2-(trifluoromethyl) benzylidene) cyclohexanone (LG13), **3**	In vivo	5 mg/kg	6 weeks	↓ Blood glucose ↑ Glucose tolerance ↓ Hepatic insulin resistance	[43]
(2E,5E)−2-(3-hydroxy-4-methoxybenzylidene)−5-(2-nitrobenzylidene) cyclopentanone, **4**	In vivo	10 mg/kg	6 weeks	↓ Blood glucose ⊥ Hyperglycaemia-induced inflammation ⊥ Hyperglycaemia-induced fibrosis	[44]
(E, E)−1,5-bis(2-bromophenyl)−1,4-pentadiene-3-one, **5**	In vivo	1, 3, and 9 mg/kg	8 weeks	↓ Serum creatinine ↓ Urea nitrogen ↓ 24 h urine protein ↓ Angiotensin II	[45]
Curcumin-based pyrano[2,3-d] pyrimidine derivatives, **6–12**	In vitro	100 μM	N/A	⊥ α-Glucosidase ⊥ α-Amylase	[46]
Curcumin-based pyrano[2,3-d] pyrimidine derivatives, **13–18**	In vitro	20 μM	N/A	⊥ α-Glucosidase ⊥ α-Amylase	[47]
Curcumin pyrazole derivatives, **19–23**	In vitro	400 and 800 μMol/L	N/A	↑ Glucose uptake ⊥ α-Glucosidase ⊥ α-Amylase ⊥ Sucrase	[48]
Water-soluble curcumin derivative **(NCD)**	In vivo	10 mg/kg	45 days	↓ Plasma glucose ↑ Plasma insulin ↓ Serum triglycerides ↓ Serum cholesterol ↓ Serum LDL ↑ Serum HDL	[49]

Note: Symbol key: ↓ decreased; ↑ increased; ⊥ inhibited.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable.

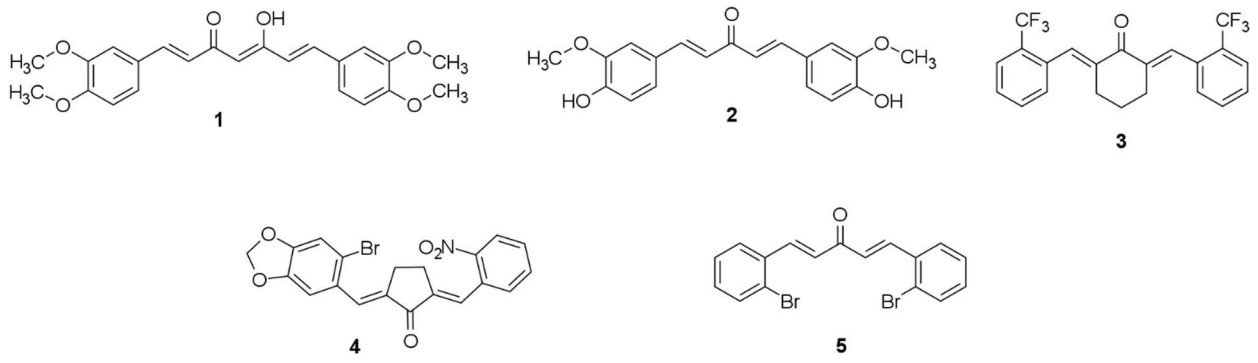

FIGURE 2 | Chemical structures of synthetic curcumin Compounds **1–5** [42–45].

maintaining insulin sensitivity via the PI3K/Akt pathway. Moreover, it upregulated hepatic GLUT-4, IRS-1, and adiponectin expression while downregulating FABP-4 [43]. The inclusion of electron-withdrawing trifluoromethyl groups and a rigid cyclohexanone linker likely enhanced lipophilicity, stability, and receptor binding affinity, accounting for the superior pharmacological activity compared to the reference drugs. These findings highlight how structural fluorination and ring constraint can

simultaneously improve bioavailability and signal-pathway modulation in antidiabetic agents.

Chen et al. [44] synthesised (2E,5E)−2-(3-hydroxy-4-methoxybenzylidene)−5-(2-nitrobenzylidene)-cyclopentanone (**4**) (Figure 2) to investigate its ability to mitigate diabetic complications. Oral treatment (10 mg/kg) of Compound **4** for 6 weeks markedly reduced hyperglycaemia-induced inflammation, hypertrophy, and fibrosis in diabetic mice, leading to improved renal and cardiac function markers. The nitro-substituted benzylidene moiety of the compound was proposed to increase electron-withdrawing capacity, thereby suppressing pro-inflammatory cytokines such as TNF-α and IL-6, while the methoxy group preserved antioxidant function. Compared with curcumin administered at 50 mg/kg, Compound **4** achieved greater glycaemic control and tissue protection at a much lower dose (10 mg/kg), suggesting that asymmetrical substitution confers dual anti-inflammatory and antioxidant benefits through complementary electronic effects.

Similarly, Xu et al. [45] reported the synthesis of (E,E)−1,5-bis (2-bromophenyl)−1,4-pentadiene-3-one (**5**) (Figure 2) and evaluated its protective effect on diabetic nephropathy in streptozotocin-induced rats. Treatment with 1–9 mg/kg of Compound **5** for 8 weeks significantly lowered serum creatinine, urea nitrogen, and 24-h urinary protein compared with untreated diabetic controls. Notably, the compound reduced circulating angiotensin II (Ang II) levels, the principal effector of the renin–angiotensin system responsible for promoting renal fibrosis and hypertension [50]. The bromine substituents of the derivative may have enhanced redox stability and improved protein–ligand interactions with redox-sensitive enzymes, thereby reducing oxidative and fibrotic damage in renal tissues. Acute toxicity studies revealed that oral administration up to 3 g/kg was well tolerated without mortality or observable adverse effects, indicating a favourable safety profile for further preclinical exploration [45].

Hasaninezhad et al. [46] provided additional insights into alternative mechanisms through which synthetic curcumin derivatives may exert antidiabetic effects. The study evaluated the in vitro antidiabetic activity of several novel pyrano [2,3-d] pyrimidine derivatives of curcumin (Compounds **6–12**; Figure 3), focusing on their inhibitory effects on two key carbohydrate-metabolising enzymes: α-amylase and α-glucosidase.

A study showed that the inhibition of these enzymes resulted in a reduction of postprandial hyperglycaemia in diabetic individuals, ultimately reducing intestinal glucose absorption [50], as observed in the standard antidiabetic drug, acarbose (Figure 4).

The synthetic curcumin derivatives (Compounds **6–12)** exhibited a more potent inhibitory effect on yeast α-glucosidase than acarbose, a standard antidiabetic drug, with an IC_{50} value of 206.57 mM [46]. Kinetic analyses, based on Lineweaver–Burk and Cortés plots, indicated that the mode of inhibition was competitive. However, the curcumin derivatives showed less effectiveness in inhibiting α-amylase enzyme compared to acarbose, with 42% inhibitory activity. This is advantageous because a strong pancreatic α-amylase inhibition can result in abnormal colon fermentation of carbohydrates, leading to diarrhoea and flatulence. Therefore, a drug candidate that strongly inhibits α-glucosidase and weakly or moderately inhibits pancreatic α-amylase is considered a potent antidiabetic agent [46].

Similarly, Mehrabi et al. [47] synthesised 13 pyrano[2,3-d] pyrimidines derivatives of curcumin by reacting equal amounts of curcumin with barbituric acid and aldehydes, using borax as a catalyst. Additionally, ethanol served as the solvent in this reaction and their inhibitory potentials against α-glucosidase and α-amylase were tested. At a uniform concentration of 20 μM, six of the derivatives, Compounds **13–18** (Figure 5), exhibited a stronger inhibition of α-glucosidase than curcumin by 82%, 77%, 76%, 73%, 71%, and 68%, respectively. However, Compound **14**, with an IC_{50} value of 18 μM, exhibited inhibitory activity that was closest to that of acarbose ($IC_{50} = 14$ μM). Based on this comparison, the study concluded that Compound **14** is a more effective inhibitor of α-glucosidase than curcumin, highlighting its potential as a promising antidiabetic agent. In addition, the compound demonstrated the highest inhibitory activity against α-amylase, with an IC_{50} value of 20.3 ± 1.3 μM, also closely aligning with that of acarbose (14.8 ± 1.4 μM). Enzyme kinetic analysis using Lineweaver–Burk plots revealed that Compound **14** competitively inhibits α-glucosidase. A molecular docking study conducted to support the experimental bioassays also confirmed that Compound **14** had the strongest binding affinity to the enzymes' active sites, corroborating its potent inhibitory activity. Furthermore, most of the tested compounds exhibited greater chemical stability than curcumin, with Compounds **15** and **18** showing the highest stability at 97% and 98%, respectively.

Glucose uptake is a crucial metabolic process that facilitates the absorption of glucose from the bloodstream and its usage by the cells, primarily regulated by insulin through a cascade reaction. Therefore, any compound that effectively improves glucose uptake can ultimately assist in lowering blood glucose in diabetic individuals [51]. Puneeth and Sharada [48] investigated the antidiabetic potential of curcumin pyrazole derivatives (Compounds **19–23**; Figure 6) through in vitro assays, which included evaluating glucose uptake in the porcine diaphragm and assessing their inhibitory effects on rat intestinal α-glucosidase, α-amylase, and sucrase. At concentrations of 400 and 800 μmol/L, all compounds significantly increased glucose uptake in the porcine diaphragm relative to the control, with further enhancement observed in the presence of insulin. In addition, the derivatives exhibited concentration-dependent inhibition of key carbohydrate-hydrolysing enzymes. Compound **20** demonstrated the strongest inhibition of α-glucosidase, achieving 75.29% inhibition at 200 μmol/L, exceeding that of curcumin (71.98%) at the same concentration. Compound **19** also showed substantial activity, inhibiting the enzyme by 70.53%. While the remaining derivatives exhibited moderate effects, Compounds **19** and **20** showed significant inhibition of α-amylase at 200 μmol/L, with 71.98% and 80.02%, respectively, comparable to the enzyme inhibition by curcumin (84.33%). Against sucrase, Compound **20** recorded the highest inhibition (75.82%), comparable to curcumin's 81.04%, while the other compounds displayed moderate inhibitory effects.

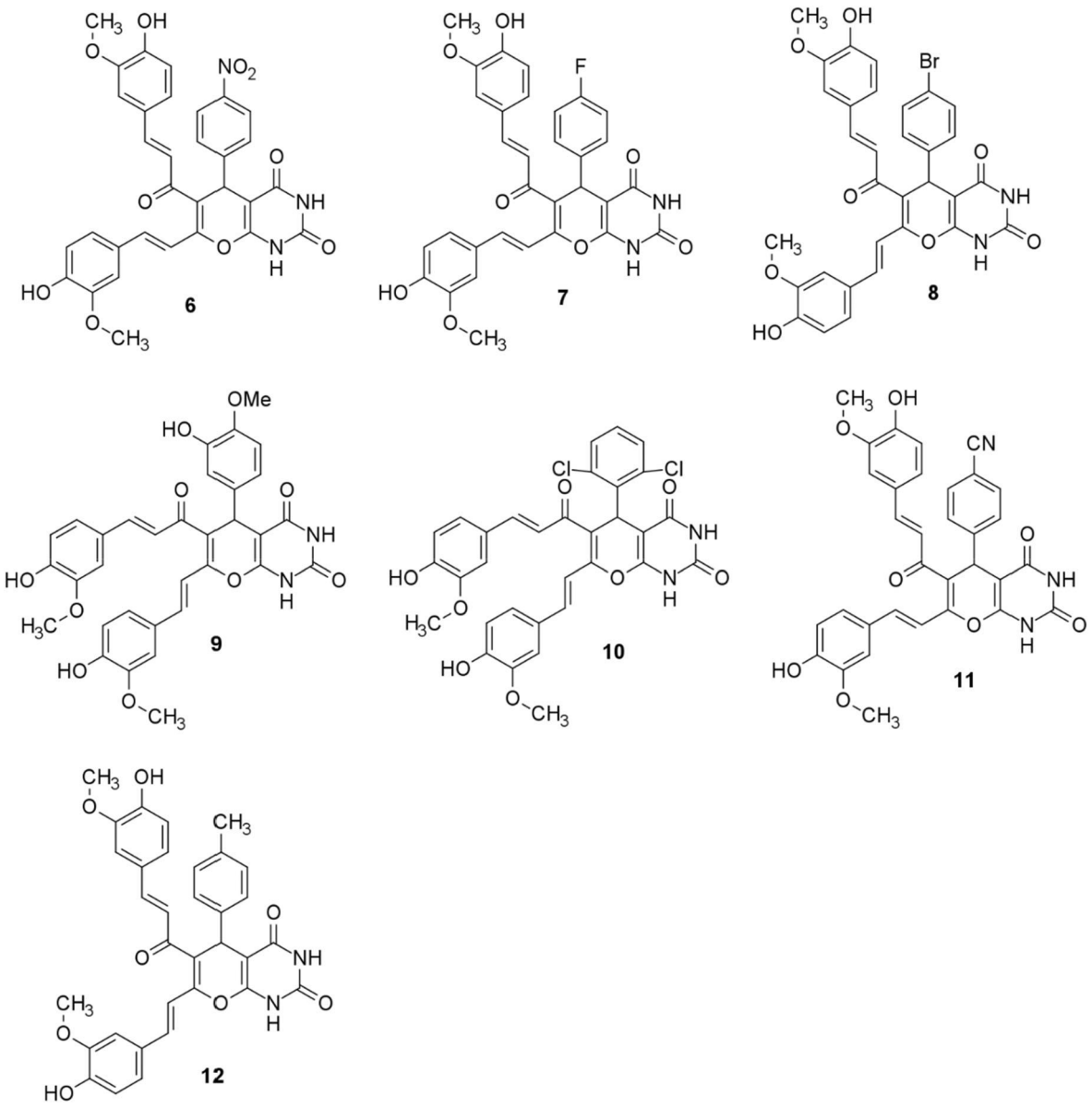

FIGURE 3 | Chemical structures of pyrano[2,3-d] pyrimidines derivatives of curcumin, **6–12** [46].

Another notable study by Abdel Aziz et al. [49] examined the antidiabetic properties of a novel water-soluble derivative of curcumin codenamed **'NCD'** on STZ-induced diabetic rats. The curcumin derivative was synthesised by covalently modifying curcumin molecule at sites different from its natural functional groups. The oral administration of 10 mg/kg of **NCD** to diabetic rats for 45 days significantly decreased their mean plasma glucose level by 27.5% when compared to the untreated diabetic group. It also significantly increased the mean plasma insulin level of diabetic rats compared to the untreated diabetic control group. Previous studies had reported curcumin's ability to enhance pancreatic β-cells function [52–54]. Considering the curcumin base of **NCD**, the study concluded that the enhancement of pancreatic β-cell function is responsible for **NCD**'s ability to significantly increase the plasma insulin of diabetic rats and may be one of the mechanisms for its hypoglycaemic activity. Since hyperlipidaemia is a common complication of diabetes mellitus, the study also evaluated how **NCD** treatment impacted the main indicators of hyperlipidaemia in diabetic rats, such as an increase in cholesterol, serum triglycerides, and LDL, along with a reduction in serum HDL. NCD administration led to significant reductions in cholesterol, serum triglycerides, and LDL levels, along with increased HDL levels in diabetic rats.

4 | Anticancer Properties of Curcumin Derivatives

Cancer treatment is of different types and depends on the cancer stage and type. Cancer treatment ranges from chemotherapy, where drugs are used to target and kill the cancer cells, to hormone therapy, which is targeted at specific cancer types that require hormones to grow, e.g., breast and prostate cancer [55]. Other cancer treatment options include hyperthermia (which utilises high heat to damage and kill cancer cells, with minimal effect on normal tissues), immunotherapy (activation of the immune system of the body to combat cancerous cells), photodynamic therapy (use of light-activated drugs to target

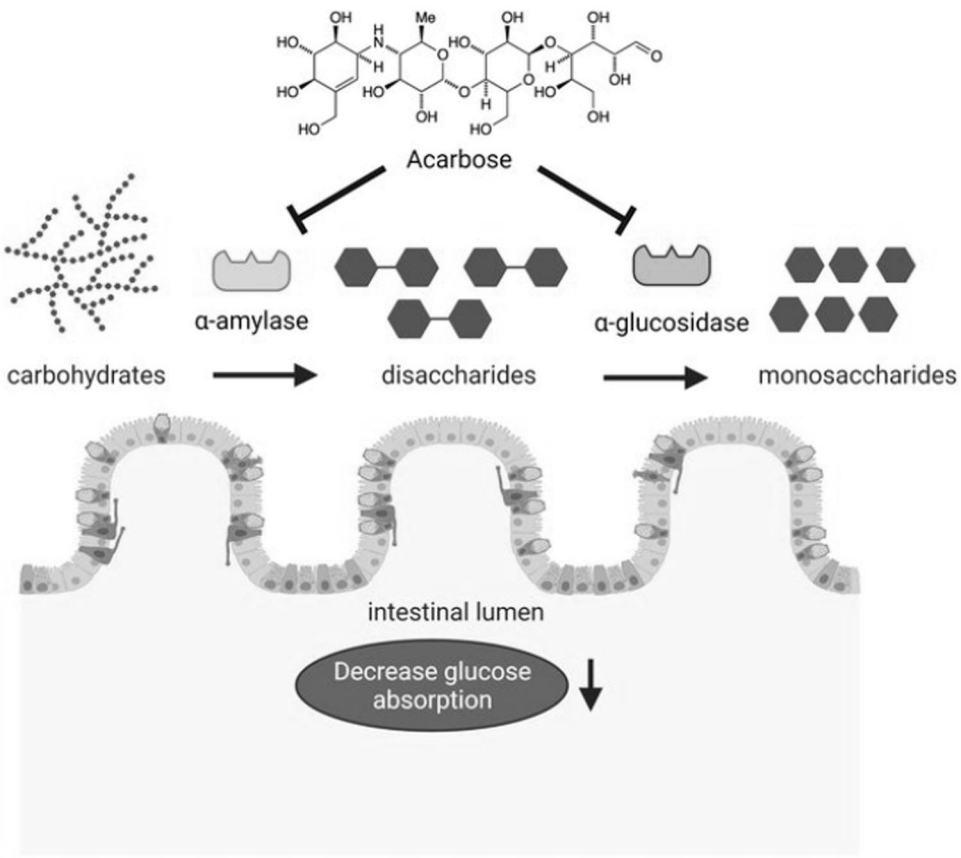

FIGURE 4 | Mechanism of action of acarbose as an α-amylase and α-glucosidase inhibitor [50].

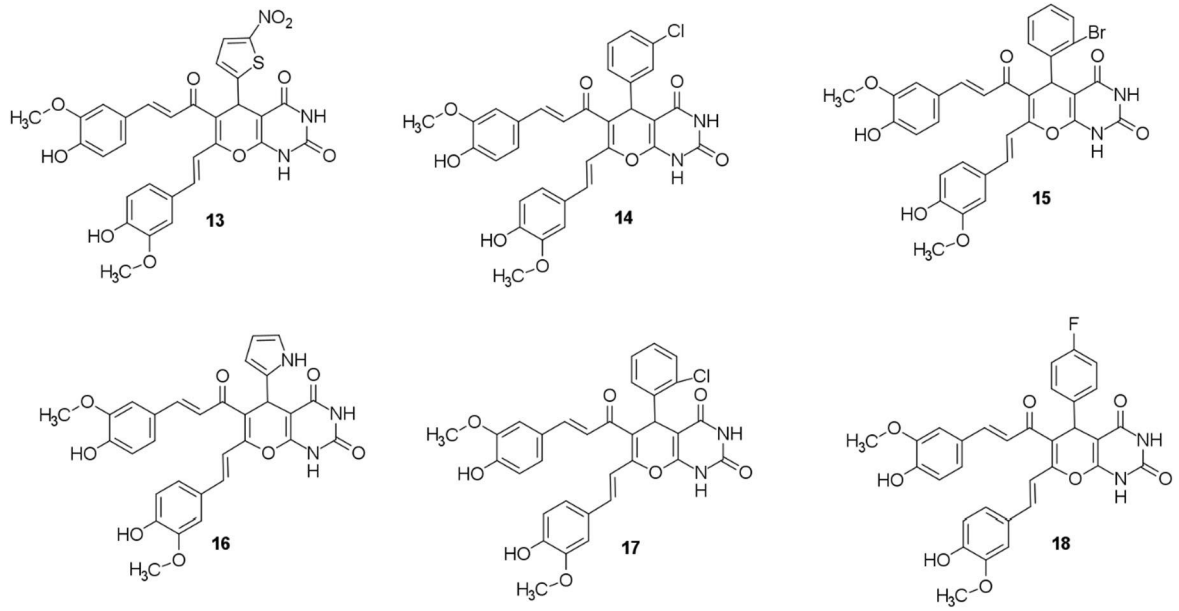

FIGURE 5 | Chemical structures of pyrano[2,3-d] pyrimidines derivatives of curcumin, **13–18** [47].

cancerous cells), radiation therapy (usage of high radiation to shrink and kill cancer cells) and the surgical removal of cancerous tumours [55]. While recent advances have improved cancer therapy, adverse effects such as nausea, fatigue, and immunosuppression remain prevalent [56]. These side effects have the potential to impact a cancer patient's quality of life and could escalate to life-threatening situations, like neutropenic infections in severe instances [56]. Neutropenic infections occur due to a depletion in the leukocytes, which are the primary defence against infections in the body. The search for an effective cancer treatment with minimal side effects has led to the screening of several medicinal plants for their anticancer properties [57]. Among them, curcumin and its synthetic derivatives have featured prominently due to their very low toxicity

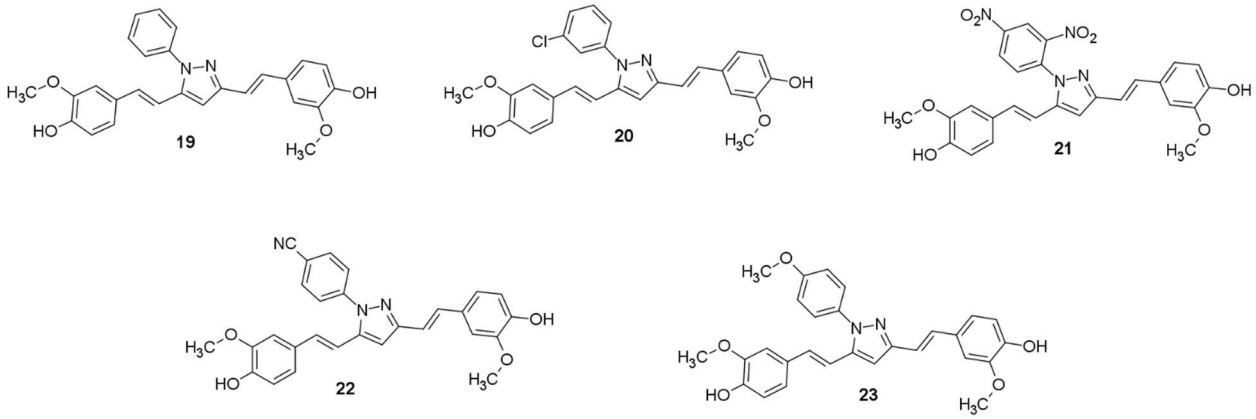

FIGURE 6 | Chemical structures of pyrazole derivatives of curcumin, **19–23** [48].

[28, 29, 32, 36, 58]. A summary of research detailing their anticancer properties is presented in Table 2.

Lai et al. [59] explored the impact of a curcumin analogue, 5-hydroxy-1,7-bis(3,4-dimethoxyphenyl)−1,4,6-heptatrien-3-one (ASC-J9), **24** (Figure 7), in suppressing castration-resistant prostate cancer (CRPC) cells, a drug-resistant form of prostate cancer, by targeting the androgen receptor (AR). Androgens facilitate prostate cancer cells' growth by activating AR. While androgen deprivation therapy (ADT), which lowers androgen levels or inhibits AR, is effective for some prostate cancers, CRPC remains resistant and continues to grow despite reduced androgen levels [66].

Lai et al. [59] investigated Compound **24**'s effect on prostate cancer using in vitro and in vivo models. In vitro, at 5 and 10 μmol/L concentrations, it selectively degraded the AR in prostate cancer cells by disrupting its interaction with coregulators like ARA55 and ARA70. This degradation occurred through the proteasome-dependent pathway over 24–48 h. Additionally, it significantly inhibited both androgen-sensitive and CRPC cells' growth when tested over 6 days. It also disrupted AR-mediated transcriptional activity by interfering with key signalling processes. In vivo, Compound **24** was administered at 75 mg/kg body weight, every other day for 14 days to castrated nude mice xenografted with CRPC cells, and it significantly reduced tumour proliferation. In non-castrated nude mice, the compound, administered at 50 or 100 mg/kg body weight twice per week, either immediately after xenograft implantation, or 2–3 weeks later, effectively inhibited tumour progression over 4 weeks. The study further demonstrated the compound's chemopreventive effects in suppressing tumour initiation and progression in the TRAMP and PTEN+/− genetically engineered mouse models, which spontaneously develop prostate cancer, with daily doses of 75 mg/kg in TRAMP mice and 100 mg/kg three times per week in PTEN+/− mice, over periods of 16 weeks and 2 months, respectively. Throughout these studies, Compound **24** was reported to be well-tolerated, with mice maintaining normal body weights, serum testosterone levels, and sexual activity, indicating minimal toxicity and few adverse effects [59].

In a related research, Cheng et al. [60] investigated the interaction of Compound **24**, solubilized in FDA-approved solvents (DMSO and PEG-400), with prostate cancer cells. The compound (0–40 μM) demonstrated an effective inhibition of prostate cancer cell growth with a low IC_{50} value of 9.0 μM in AR-positive cells, in vitro. In a mouse model, Compound **24** orally administered (200 mg/kg) on alternate days for 16 days, successfully suppressed CRPC tumour growth without significant side effects. The study concluded that the compound's effectiveness in suppressing prostate cancer growth, while dissolved in FDA-approved solvents, could be significant for its potential use in human clinical trials.

Another study by Ding et al. [61] also provided insights into the anticancer properties of synthetic curcumin derivatives. The study synthesised series of water-soluble derivatives of curcumin—etherified, esterified, and phosphorylated—and tested the in vitro anticancer effects on hepatocellular carcinoma Hep-G2, human breast cancer MCF-7, and human cervical carcinoma HeLa cells [61]. Their stability in rabbit plasma was also assessed in vitro. All the compounds at varying concentrations (2.5–80 μM) were reported to have strong inhibition on all the cancer cell lines after 72 h treatment. However, a particular phosphorylated derivative named 4-((1E,6E)−7-(4-hydroxy-3-methoxyphenyl)−3,5-dioxohepta-1,6-dienyl)−2-methoxyphenyldihydrogen phosphate, **25** (Figure 7) had the highest inhibition activity with an IC_{50} of 6.78 μM against HeLa cells as against curcumin with an IC_{50} of 17.67 μM. The derivatives also induced apoptosis in cancer cells in a dose-dependent manner, evidenced by nuclear shrinkage and fragmentation. Stability tests showed that some of the derivatives were highly stable in plasma. Some of them, including Compound **25**, slowly released curcumin in plasma, potentially maintaining therapeutic levels longer and enhancing their antitumor efficacy. These findings suggest that the synthesised derivatives possess enhanced anticancer activity, solubility, and stability compared to curcumin, indicating their potential as effective anticancer agents.

Similarly, a study synthesised some novel curcumin derivatives (Compounds **26–27**) through the chemical condensation of curcumin with chalcones, a class of bioactive compounds present in fruits and vegetables [62]. The bioactivities of these derivatives, termed 'curcuminoid chalcones', were evaluated against human colon carcinoma (Caco-2) cells using the resazurin reduction and lactate dehydrogenase (LDH) release

TABLE 2 | Summary of anticancer properties of curcumin derivatives.

Curcumin derivative	Study type	Cancer type	Dosage	Treatment duration	Mechanism	References
5-Hydroxy-1,7-bis(3,4-dimethoxyphenyl)−1,4,6-heptatrien-3-one (ASC-J9), **24**	In vitro	Prostate cancer	5 and 10 μmol/L	1–6 days	↓ AR protein ↓ Prostate cancer cell growth ⊥ AR-mediated transcription	[59]
	In vivo		50, 75, and 100 mg/kg	2–4 weeks	↓ Tumour initiation and progression	
5-Hydroxy-1,7-bis(3,4-dimethoxyphenyl)−1,4,6-heptatrien-3-one (ASC-J9), **24**	In vitro	Prostate cancer	0–40 μM	24 h	↓ AR-positive prostate cancer cells growth	[60]
	In vivo		200 mg/kg	16 days	↓ CRPC tumour growth	
4-((1E,6E)−7-(4-hydroxy-3-methoxyphenyl)−3,5-dioxohepta-1,6-dienyl)−2-methoxyphenyldihydrogen phosphate, **25**	In vitro	Human breast cancer (MCF-7 cells). Hepatocellular carcinoma (Hep-G2 cells). Human cervical carcinoma (HeLa cells)	2.5–80 μM	72 h	↓ Cancer cell growth Apoptosis induction	[61]
(E-3-(4-hydroxy-3-methoxyphenyl)−1-phenylprop-2-en-1-one), **26** and E-1,3-bis(4-hydroxy-3-methoxyphenyl)−1-phenylprop-2-en-1-one, **27**	In vitro	Human colon carcinoma (Caco-2) cell	1 nM–100 μM	24–48 h	↑ ROS production ↑ HO1 expression ↓ CAT expression	[62]
Metallo-curcumin-conjugated DNA complexes, **28**	In vitro	Prostate cancer	80 μM–4 mM	24–48 h	↓ Human prostate cancer cell growth	[63]
Curcumin-fluorouracil (Cur-5-FU) hybrid derivative, **29**	In vitro	A549 lung cancer cells 4T1 breast cancer cells	0–100 μM	48 h	↓ Cancer cell growth ⊥ Thioredoxin reductase (TrxR) and thymidylate synthase (TS)	[64]
	In vivo	4T1 breast cancer cells	4, 8, and 12 mg/kg	14 days	↓ Volume and weight of tumour tissue	
(1E,6E)−1-(3-methoxy-4-2'-nitroxyethoxyl)-4-(2-thienylmethylene)−7-(3-methoxy-4-2'-nitroxyethoxyl) hepta-1,6-diene-3,5-dione, **30**	In vivo	MCF-7 breast cancer cells	1.5 and 3.0 μmol/L	24 h	Induced apoptosis and G2/M cell cycle arrest ↓ P13K expression ↑p53, cleaved caspase-9 and caspase-3 expressions.	[65]

Note: Symbol key: ↓ decreased, ↑ increased, ⊥ inhibited.

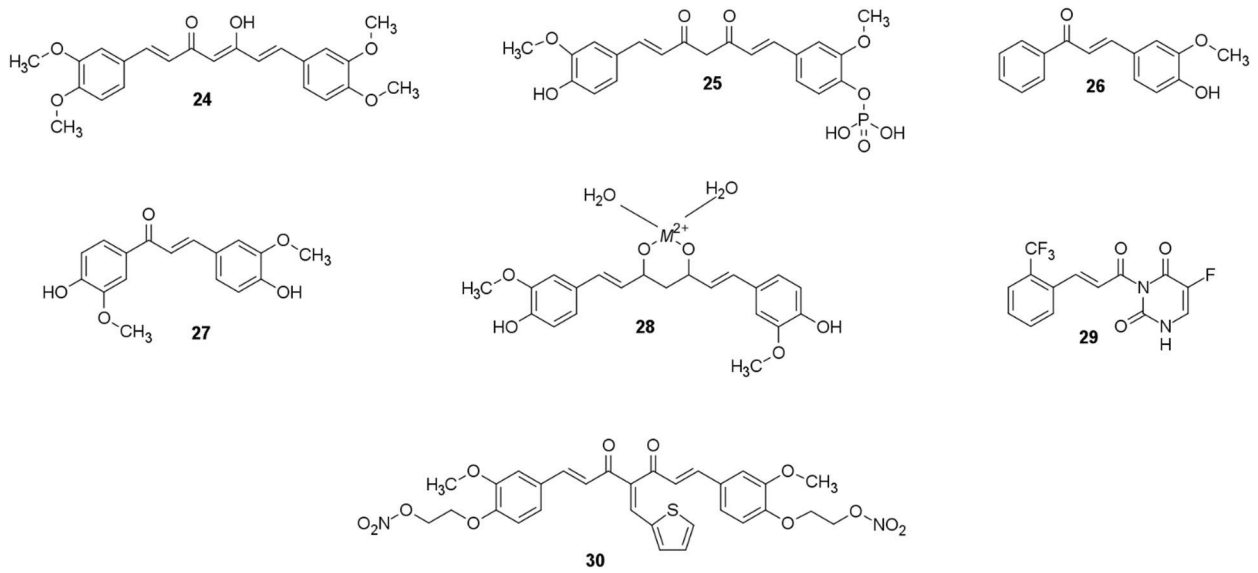

FIGURE 7 | Chemical structures of synthetic curcumin Compounds **24–30** [59, 61–65] (M^{2+} in **28** represents Cu^{2+}, Ni^{2+}, or Zn^{2+}).

assays. Compounds **26** (E-3-(4-hydroxy-3-methoxyphenyl)−1-phenylprop-2-en-1-one) and **27** (E-1,3-bis(4-hydroxy-3-methoxyphenyl)−1-phenylprop-2-en-1-one) (Figure 7) at a concentration range of 1 nM–100 μM exhibited the most significant cytotoxicity against the Caco-2 cell line. At the highest concentration of 100 μM, Compounds **26** and **27** achieved a significant resazurin reduction of 63.59% and 63.60% respectively, compared to control after 48 h of exposure to Caco-2 cells. Compounds **26** and **27** at 100 μM concentration also increased the LDH release level in the cells by 97.92% and 87.92% respectively, over 48 h period. Both compounds were reported to have significantly increased reactive oxygen species (ROS) production in a concentration-dependent manner, relative to control, which led to cell death. These compounds also decreased the expression of the catalase (*CAT*) gene while increasing the expression of heme oxygenase-1 (HO-1). The study concluded that Compounds **26** and **27** possess potential anticancer activity, attributed to their capacity to induce oxidative stress in human colon carcinoma (Caco-2) cells [62].

In another study, Vellampatti et al. [63] explored the anticancer potential of synthetic curcumin derivatives by formulating metallo–curcumin–conjugated DNA complexes incorporating Cu^{2+}, Ni^{2+}, and Zn^{2+} ions. These complexes were designed as innovative drug delivery systems for targeted therapy against prostate cancer. The metallo-curcumin complexes, **28** (Figure 7), were made up of 80 μM of curcumin combined with either 4 mM of Cu^{2+}, 2 mM of Ni^{2+}, or 1 mM of Zn^{2+}. Their anticancer activity was tested against the cell viability profiles of five distinct prostate cancer cell lines: DU145 (human prostate carcinoma derived from brain metastasis), LNCaP (human metastatic prostate carcinoma from lymph nodes), PC3 (human prostate cancer cells from bone metastasis), 22Rv1 (human prostate carcinoma from bone metastasis), and TRAMP-C1 (a transgenic adenocarcinoma mouse prostate model). These complexes showed enhanced cytotoxicity against prostate cancer cells by improving curcumin's solubility and binding affinity through DNA groove binding and electrostatic interactions. The study demonstrated that Cu^{2+}-curcumin conjugates exhibited the highest cytotoxic effects (83%–96%) across all prostate cancer cell lines, with greater efficacy observed after 48 h. The research also highlighted the potential of these metallo-curcumin complexes to act as antibacterial agents, further broadening their therapeutic applications.

A recent research by Wang et al. [64] investigated the anticancer properties of some novel curcumin-fluorouracil (Cur-5-FU) hybrid derivatives. Among the derivatives synthesised, Compound **29** (Figure 7) demonstrated the most potent anticancer effects. In vitro studies revealed that the compound significantly inhibited the growth of A549 lung and 4T1 breast cancer cells with IC_{50} of 3.59 and 1.29 μM, respectively, and a favourable selectivity index (SI > 10) compared to normal cells. In unravelling the compound's mechanism of action, the study reported that the derivative targeted two key proteins, thioredoxin reductase (TrxR) and thymidylate synthase (TS), both of which are vital for cancer cell survival. TrxR, an enzyme that helps cancer cells manage oxidative stress by reducing thioredoxin, is often overexpressed in tumours [67]. Compound **29** binds to the active site of TrxR, specifically interacting with critical residues like Sec. 498 and Cys497, inhibiting its activity, which led to ROS accumulation. The resulting oxidative stress pushes cancer cells past their survival threshold, triggering apoptosis. In parallel, the compound also targeted TS, a key enzyme in DNA synthesis, by inhibiting its function, thereby blocking DNA replication and causing cell cycle arrest in the G_0/G_1 phase. This dual inhibition disrupts both redox homeostasis and DNA synthesis, making the compound highly effective in inducing cancer cell death. In vivo experiments in mice confirmed the compound's ability to significantly reduce tumour volume at dosages of 4, 8, and 12 mg/kg for 14 days, with minimal side effects. The combination of selective targeting of TrxR and TS underscores the compound's potential as a lead compound for cancer treatment.

Zhou et al. [65], in another recent study, developed some novel curcumin derivatives and evaluated their cytotoxic effect on five human tumour cell lines, A549, HeLa, HepG2, MCF-7, and HT-

29. The phenolic groups of curcumin were substituted with nitrooxy group to synthesise the compounds. Among the derivatives, a compound named (1E,6E)−1-(3-methoxy-4-2'-nitroxyethoxyl)-4-(2-thienylmethylene)−7-(3-methoxy-4-2'-nitroxyethoxyl) hepta-1,6-diene-3,5-dione, **30** (Figure 7) had the most anticancer activity in vitro with an IC_{50} of 6.78, 1.03, 1.21, 1.39, and 1.45 μmol/L against HeLa, A549, HepG2, MCF-7, and HT-29 tumour cells, respectively. The cytotoxic effect of Compound **30** against the cell lines were several folds higher than curcumin and standard anticancer drug, cisplatin. To further evaluate the mechanism of action of the compound's cytotoxic effect against MCF-7 breast cancer cells, several assays, including cell cycle arrest, apoptosis, membrane potential and intracellular ROS detection, were carried out. The study concluded that Compound **30** induced apoptosis and G2/M cell cycle arrest in the MCF-7 breast cancer cells. It also decreased the gene expression of P13K and increased p53, cleaved caspase-9 and caspase-3 expressions in the cells, all of which contributed to the compound's cytotoxic potential against MCF-7 breast cancer cells [65]. The cytotoxicity of the compound was further evaluated on two non-cancerous cell lines, LO-2 and HK-2, and the result indicated that Compound **30** was non-toxic to the normal cells.

5 | Structure-Activity Relationships (SARS) of Synthetic Curcumin Derivatives

While curcumin has gained significant attention for its antidiabetic and anticancer properties, its therapeutic applications are hindered by poor bioavailability, rapid metabolism, and low aqueous solubility, limiting its efficacy in clinical settings. To overcome these challenges, researchers have explored structural modifications aimed at improving curcumin's pharmacokinetics and pharmacodynamics. These modifications not only enhance efficacy and selectivity but also improve stability, solubility, and metabolic resistance. A critical evaluation of these derivatives is presented in Table 3, which not only summarises their structural modifications and biological activities but also highlights their primary mechanistic targets, reported strengths, and inferred limitations. For instance, the strategic methoxylation of phenolic hydroxyl groups of curcumin as observed in Compounds **1** and **2** increased their lipophilicity and metabolic stability, facilitating enhanced membrane permeability and prolonged plasma half-life [42]. Furthermore, incorporating conjugated dienone moieties preserved the β-diketone pharmacophore essential for their antioxidant and anti-inflammatory activity, pivotal in mitigating oxidative stress-induced β-cell dysfunction and insulin resistance. The electron-donating methoxy groups likely modulated the electron density distribution across the aromatic rings, thereby strengthening π-π interactions with key enzymatic targets in glucose metabolism.

Also, Zhao et al. [43] reported the synthesis of a curcumin analogue, LG13 (Compound **3**), designed to selectively inhibit 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a pivotal enzyme involved in glucocorticoid activation and hepatic gluconeogenesis. The introduction of the trifluoromethyl groups onto the benzylidene moieties significantly enhanced the compound's lipophilic character, facilitating blood–brain barrier penetration and increasing binding affinity to the hydrophobic pocket of 11β-HSD1. The cyclohexanone linker further contributed to the molecular rigidity and improved pharmacokinetics of the compound, indicating that incorporation of electron-withdrawing groups can selectively modulate enzymatic interactions to augment therapeutic outcomes. Similarly, the incorporation of a nitro group on the benzylidene moiety of curcumin, as observed in Compound **4,** enhanced the compound's electron-withdrawing capacity, which potentiated the suppression of pro-inflammatory cytokines such as TNF-α and IL-6 under hyperglycaemic conditions. Meanwhile, the hydroxy and methoxy substitutions on the opposing aromatic ring facilitated free radical scavenging, contributing to the attenuation of oxidative stress-induced fibrosis in renal and cardiac tissues [44]. This bifunctional architecture demonstrates the importance of asymmetrical substitution in achieving dual mechanistic actions of anti-inflammatory and antioxidant effects.

In another advancement, Xu et al. [45] evaluated the brominated curcumin analogue, Compound **5**, for its protective effects on renal function in streptozotocin-induced diabetic rats. Halogenation of curcumin with bromine atoms increased its molecular stability and enhanced the compound's redox potential. The bromo-substituted phenyl rings likely contributed to stronger binding affinities with redox-sensitive proteins, thereby reducing oxidative stress markers and improving glomerular function. This underscores the therapeutic advantage of halogen substitutions in curcumin scaffolds for mitigating diabetic nephropathy. Two independent studies [46, 47] explored the synthesis and biological evaluation of pyrano[2,3-d] pyrimidine-based curcumin derivatives (Compounds **6–18**), which displayed significant α-amylase and α-glucosidase inhibitory activity in vitro. The fused pyranopyrimidine rings of the compounds provided increased molecular rigidity and aromaticity, enhancing the orientation and binding stability within the active sites of the digestive enzymes. Similarly, Puneeth and Sharada [48] synthesised a series of curcumin pyrazole derivatives (Compounds **19–23**) and assessed their in vitro antidiabetic activity. Introduction of the pyrazole moiety conferred increased metabolic resistance, likely due to steric hindrance around the β-diketone region, reducing rapid reduction and conjugation by hepatic enzymes. These derivatives demonstrated notable glucose uptake effect and concentration-dependent inhibition of key carbohydrate-hydrolysing enzymes, such as α-amylase, α-glucosidase and sucrase. Abdel Aziz et al. [49] also reported the development of a water-soluble curcumin derivative **(NCD)**, through the covalent modification of curcumin molecule at sites different from its natural functional groups, which significantly improved glycaemic control in experimental type 1 diabetic rats. The increased aqueous solubility translated to superior bioavailability, facilitating rapid systemic absorption and immediate pharmacological action. **NCD** demonstrated enhanced insulin secretion and reduced serum glucose levels within a short treatment window. This modification validates the SAR principle that solubility enhancement, even without core structural changes, can dramatically improve pharmacodynamic outcomes.

Additional structural modifications of curcumin, such as hydroxylation and methoxylation, have also been explored to enhance its therapeutic efficacy. A prominent example is ASC-

TABLE 3 | Synthetic curcumin derivatives: structural modifications, mechanistic targets, strengths, and limitations in diabetes and cancer models.

Compounds	Structural modification	Primary mechanism/ target pathway	Strengths	Limitations	References
1–2	Methoxylation of phenolic OH groups	Antioxidant activity; β-cell protection	↑ Lipophilicity, metabolic stability, membrane permeability, and half-life	Limited translation from in vitro to in vivo	[42]
3	Trifluoromethyl substitution + cyclohexanone linker	Akt/PI3K pathway activation; ⊥ 11β-HSD1; ↑ GLUT-4, IRS-1	Superior in vivo antidiabetic activity compared with pioglitazone; good pharmacokinetics	Evaluation limited to preclinical models; human safety data not available	[43]
4	Nitro substitution + hydroxy/ methoxy groups	Suppresses TNF-α, IL-6; antioxidant	↓ Pro-inflammatory cytokines; attenuated oxidative stress, fibrosis in renal/cardiac tissue	Nitro substituents are generally associated with potential toxicity; long-term effects not studied	[44]
5	Bromination	↓ Ang II; ↑ redox protein interaction	Improved renal function in diabetic rats; reduced oxidative stress; safe at doses up to 3 g/kg	Evidence limited to nephropathy model; no data on other diabetic complications	[45]
6–18	Pyrano[2,3-d] pyrimidine conjugation	⊥ α-Amylase & α-glucosidase	Strong in vitro inhibition of digestive enzymes; improved molecular rigidity and binding stability	No in vivo validation; activity limited to enzyme assays	[46, 47]
19–23	Pyrazole conjugation	Enhances glucose uptake; inhibits α-glucosidase, α-amylase, and sucrase	Steric hindrance increased metabolic resistance; improved enzyme inhibition	Results limited to in vitro enzyme inhibition; no pharmacokinetic data	[48]
NCD	Covalent modification	↑ Insulin secretion; ↓ serum glucose	Greatly improved solubility; enhanced glycaemic control and lipid profile in type 1 diabetic rats	Stability under physiological conditions not confirmed; long-term effects unclear	[49]
24	Methoxylation + hydroxylation	Androgen receptor (AR) degradation; ⊥ NF-κB	Selectively degraded AR; reduced castration-resistant prostate cancer (CRPC) progression	Preclinical data only; requires human trials	[59, 60]
25	Phosphorylation	↑ Caspase-3; apoptosis induction	Superior anticancer potency vs. curcumin (IC_{50}: 6.78 μM vs. 17.67 μM in HeLa); improved solubility and plasma stability	No in vivo validation; pharmacokinetic complexity (slow release may hinder dosing and consistent therapeutic levels)	[61]
26–27	Chalcone conjugation	↑ ROS production and HO-1 expression; ↓ catalase expression	Induced ROS-mediated apoptosis in colon cancer cells	Selectivity towards cancer vs. normal cells not fully established	[62]

(Continues)

TABLE 3 | (Continued)

Compounds	Structural modification	Primary mechanism/ target pathway	Strengths	Limitations	References
28	Metal conjugation with Cu^{2+}, Ni^{2+}, Zn^{2+}	DNA intercalation; ROS-mediated apoptosis	Cu^{2+} complex showed high (83%–96%) anticancer potency; enhanced solubility and stability	Long-term toxicity of metals not assessed	[63]
29	Fluorouracil conjugation	⊥ Thioredoxin reductase (TrxR) and thymidylate synthase (TS); ROS accumulation; apoptosis induction	Dual-targeting strategy; high selectivity index (SI > 10)	Risk of overlapping 5-FU toxicity	[64]
30	Nitrooxy group substitution on phenolic groups	G2/M cell cycle arrest; apoptosis induction; ⊥ PI3K; p53 and caspase activation	Several-fold more potent than cisplatin; low toxicity to normal cells	Requires in vivo and clinical validation	[65]

Note: Symbol key: ↓ decreased, ↑ increased, ⊥ inhibited.

J9 (Compound **24**), a methoxylated curcumin analogue specifically designed to target AR-mediated malignancies. The introduction of hydroxyl (-OH) and methoxy (-OCH_3) groups enhances hydrophobic interactions, facilitating improved membrane permeability and intracellular accumulation. These modifications also stabilise curcumin's enol-keto tautomeric forms, thereby reducing metabolic degradation. In prostate cancer models, ASC-J9 demonstrated enhanced selectivity toward AR degradation, disrupting AR-coregulator interactions and reducing CRPC progression. This suggests that methoxylation improves both efficacy and specificity, making ASC-J9 a promising candidate for targeted therapy [59, 60]. Another notable modification is phosphorylation, which significantly enhances curcumin's aqueous solubility and plasma stability. The phosphorylated derivative Compound **25** exhibited superior anticancer potency, reflected in its lower IC_{50} value (6.78 μM against HeLa cells) compared to curcumin (17.67 μM). This improvement is attributed to phosphate-mediated prodrug activation, which allows for controlled hydrolysis in plasma, resulting in a sustained release of the active compound. Furthermore, phosphorylation enhances curcumin's interaction with key apoptotic pathways, facilitating increased caspase-3 activation and mitochondrial membrane disruption, leading to higher apoptotic rates in cancer cells [61]. This modification is particularly beneficial for drug formulations requiring systemic administration, as it prolongs circulating half-life and bioavailability.

In addition to improving solubility, structural modifications involving chalcone condensation have been explored to increase curcumin's electrophilic nature, thereby enhancing its ability to interact with cellular biomolecules. The introduction of chalcone moieties in curcuminoid derivatives (Compounds **26** and **27**) leads to an increase in ROS generation, which induces oxidative stress-mediated apoptosis in cancer cells [62]. The electrophilic α, β-unsaturated carbonyl system in chalcones promotes Michael addition reactions with cellular thiols, disrupting redox homeostasis. As a result, curcuminoid chalcones exhibit enhanced cytotoxicity against colon cancer cells, making them potential leads for developing novel chemotherapeutic agents [62]. Another approach to enhancing curcumin's efficacy is metal complexation, wherein curcumin is conjugated with transition metal ions (Cu^{2+}, Ni^{2+}, Zn^{2+}). These metal-curcumin complexes (Compound **28**) exhibit improved solubility, stability, and target specificity due to the formation of stable enol-keto chelates. Among these, Cu^{2+}-curcumin complexes demonstrated the highest anticancer potency, likely due to ROS-mediated DNA damage and apoptosis induction. The binding of metal ions to curcumin also enhances DNA intercalation, increasing its ability to inhibit topoisomerase activity and disrupt cancer cell proliferation [63]. Such modifications hold promise in the development of metallo-curcumin derivatives with enhanced therapeutic indices. Another noteworthy modification involves fluorouracil (5-FU) conjugation (Compound **29**), which combines curcumin's antioxidant and anti-inflammatory properties with the cytotoxic effects of 5-FU. The hybrid Cur-5-FU conjugate demonstrated an improved selectivity index (SI > 10), suggesting lower toxicity toward normal cells while retaining potent anticancer activity. Mechanistically, the Cur-5-FU hybrid inhibits thioredoxin reductase (TrxR) and TS simultaneously, leading to oxidative stress, DNA damage,

and cell cycle arrest [64]. This dual-targeting approach enhances therapeutic efficacy while reducing chemoresistance, making it a promising strategy for improving the clinical application of fluoropyrimidine-based chemotherapies.

Moreover, the introduction of nitrooxy (-NO_2) groups, as seen in Compound **30**, has been shown to significantly enhance curcumin's cytotoxicity [65]. Unlike conventional curcumin derivatives, nitrooxy curcumin disrupts nitric oxide homeostasis, leading to an increased apoptotic response through p53 upregulation and caspase activation. This derivative also demonstrated strong inhibition of the PI3K/Akt survival pathway, leading to enhanced sensitivity in multiple cancer cell lines compared to both curcumin and cisplatin [65]. These findings suggest that nitrooxy-functionalized derivatives could be explored further as selective anticancer agents with improved efficacy and reduced toxicity.

Beyond the individual examples of the SARS of the various functional groups in the curcumin derivatives discussed above, several broader trends emerge regarding the influence of structural modifications on their improved pharmacological outcomes. Modifications that increase lipophilicity, such as methoxylation of phenolic hydroxyl groups (Compounds **1** and **2**) [42] or trifluoromethyl substitution in Compound **3** [43], consistently enhanced metabolic stability and membrane permeability, translating to superior in vivo activity compared to native curcumin and standard drugs. In contrast, polar modifications designed to improve solubility, such as the water-soluble derivative **NCD** [49] and phosphorylated analogue (Compound **25**) [61], significantly improved systemic bioavailability and plasma stability, enabling greater therapeutic efficacy in both metabolic and oncological models. These findings emphasise that both hydrophobic and hydrophilic substitutions can be strategically exploited, depending on whether the therapeutic goal is intracellular target engagement or systemic circulation.

The electronic properties of substituents also emerge as critical determinants of bioactivity. Electron-donating groups such as methoxy and hydroxy moieties not only stabilised the enol-keto tautomerism of curcumin but also enhanced its antioxidant potential, which is particularly valuable in oxidative stress-driven conditions like diabetes [44, 59]. In contrast, electron-withdrawing groups, including nitro [44], trifluoromethyl [43], and nitrooxy substitutions [65], potentiated inhibitory effects on pro-inflammatory cytokines (TNF-α, IL-6) and key survival pathways such as PI3K/Akt, leading to enhanced cytotoxicity and apoptosis in cancer models. These differential outcomes suggest that the electron-donating or -withdrawing character of substituents can be exploited to enhance their therapeutic activity toward either cytoprotection in metabolic disease or selective apoptosis in malignancy.

Hybridisation strategies further demonstrate the versatility of the curcumin structure. The incorporation of chalcone moieties (Compounds **26** and **27**) [62] increased electrophilic reactivity, facilitating Michael addition with cellular thiols and promoting ROS-mediated apoptosis in colon carcinoma cells. Similarly, metal-curcumin complexes (Compound **28**) [63] not only improved solubility but also introduced DNA-binding capacity through chelation, thereby amplifying cytotoxic effects in prostate cancer. Conjugation approaches, exemplified by the Cur-5-FU hybrid (Compound **29**) [64], illustrate how combining curcumin's antioxidant and anti-inflammatory properties with the chemotoxicity of fluoropyrimidines can yield dual-targeting activity against thioredoxin reductase and TS, achieving improved selectivity indices.

These SARs insights reinforce the principle that rational modifications of the curcumin structure can be systematically applied to overcome limitations of the parent compound. Lipophilic substitutions primarily enhance stability and antidiabetic efficacy, polar modifications increase systemic availability and anticancer potency, and hybridisation or conjugation strategies enable multifunctional targeting. Together, these trends provide a conceptual framework for the design of next-generation curcumin derivatives with optimised therapeutic profiles across both diabetes and cancer.

5.1 | Translational Challenges and Limitations of Synthetic Curcumin Derivatives

While the SARS analysis in the previous section highlights substantial progress in improving the biological potency, stability, and selectivity of synthetic curcumin derivatives, several limitations as highlighted in Table 3 continue to impede their translational success. Many of these derivatives exhibit promising in vitro efficacy yet fail to demonstrate comparable in vivo outcomes due to physicochemical, pharmacokinetic, toxicological, and regulatory-related challenges, which collectively determine their clinical feasibility.

A consistent limitation among most derivatives is poor bioavailability despite improved solubility or stability. For instance, methoxylated derivatives (Compounds **1** and **2**) demonstrated enhanced lipophilicity and membrane permeability, yet their efficacy has only been confirmed in vitro, with limited data on in vivo pharmacokinetics or systemic retention [42]. Likewise, Compound **24**, although effective in promoting AR degradation and inhibiting NF-κB signalling, remains confined to preclinical cancer models [59, 60]. Similarly, phosphorylated curcumin derivative (Compound **25**) achieved superior solubility and anticancer potency in vitro but has not been validated in animal models [61], and its slow-release kinetics may complicate dosing and therapeutic consistency [68]. These examples demonstrate that structural optimisation alone does not guarantee clinical viability unless accompanied by comprehensive pharmacokinetic and in vivo efficacy studies [69].

Model dependency also represents a key translational constraint. Many derivatives with strong enzymatic or cytotoxic activities, such as pyranopyrimidine (Compounds **6–18**) [46, 47], pyrazole derivatives (**19–23**) [48], and chalcone conjugates (**26–27**) [62] have been assessed predominantly in enzyme inhibition or cell-based assays, with limited or no in vivo validation. Although these compounds show promise as enzyme inhibitors or apoptosis inducers, the absence of systemic evaluation precludes assessment of absorption, distribution, metabolism, and elimination, as well as target tissue selectivity. Bridging this gap requires standardised in vivo testing protocols that correlate biochemical potency with pharmacological efficacy.

Safety and toxicological uncertainties further limit clinical translation. Several derivatives incorporate substituents such as nitro (Compound **4**) and halogen (Compound **5**) groups that, while enhancing electron-withdrawing capacity and biological activity, may pose potential toxicity risks upon chronic exposure. For example, Compound **4** effectively reduced pro-inflammatory cytokines (TNF-α and IL-6) and oxidative stress, but has not undergone long-term safety assessment [44], while Compound **5** improved renal outcomes in diabetic rats without evaluation in other diabetic complications or prolonged dosing regimens [45]. Metallo-curcumin complexes (Compound **28**) also demonstrate potent anticancer activity via ROS-mediated DNA damage, yet their long-term systemic safety and organ accumulation profiles remain undefined [63]. Such gaps highlight the need for rigorous toxicological and pharmacokinetic testing before translational advancement.

Another limiting factor is incomplete selectivity characterisation. Derivatives such as chalcone-conjugated curcuminoids (**26–27**) [62] and Cur-5-FU hybrid (Compound **29**) [64] exhibit high cytotoxicity and favourable selectivity indices in vitro; however, their safety margins in vivo remain unknown. Similarly, the nitrooxy-curcumin derivative (Compound **30**) [65], despite showing multi-fold higher potency than cisplatin and low toxicity to normal cells in culture, has yet to be evaluated in animal models to confirm selective cytotoxicity and systemic tolerance. Without such validation, extrapolation of in vitro findings to therapeutic relevance remains uncertain.

Finally, translational and regulatory barriers persist across most synthetic curcumin derivatives. None of the compounds highlighted in this review has reached clinical testing, reflecting the ongoing challenges of scalability, formulation compatibility, and intellectual property protection in drug development [70]. Many derivatives require multistep synthesis, limiting cost-efficiency and reproducibility, while their hybrid chemical nature places them in a regulatory grey area between natural product derivatives and small-molecule drugs. Progress in this field will therefore depend on coordinated efforts between relevant stakeholders such as synthetic chemists, pharmacologists, biochemists and formulation scientists to integrate chemical innovation with pharmacological validation and scalable formulation design.

6 | Interlinked Molecular Mechanisms Between Diabetes and Cancer: Therapeutic Roles of Synthetic Curcumin Derivatives

The interlinked mechanisms between diabetes and cancer provide the molecular framework through which the therapeutic potential of synthetic curcumin derivatives in these diseases can be understood. As demonstrated in Table 3, structural modifications such as methoxylation, halogenation, phosphorylation, or hybridisation not only improve pharmacokinetic properties but also dictate how these compounds interact with molecular targets. Importantly, many of these derivatives exert their activity by modulating pathophysiological processes that are common to both diseases. For example, nitro-substituted analogues (Compound **4**) [44] suppress pro-inflammatory cytokines, phosphorylated derivatives (Compound **25**) [61] enhance apoptosis via caspase activation, and chalcone conjugates (Compounds **26–27**) [62] drive ROS-mediated cytotoxicity. These mechanistic effects converge on three major pathways central to both diabetes and cancer: chronic inflammation, oxidative stress, and dysregulated signalling. The following subsections, therefore, examine how synthetic curcumin derivatives influence each of these processes, providing a framework that links their structural features to shared molecular targets in disease progression.

6.1 | Chronic Inflammation

Chronic inflammation is a unifying driver of diabetes and cancer, and curcumin derivatives demonstrate their therapeutic potential by attenuating inflammatory cytokines and transcription factors that sustain this state. Inflammation in diabetes is largely driven by metabolic stress, obesity-induced immune activation, and the accumulation of pro-inflammatory cytokines, which impair insulin signalling and disrupt glucose homeostasis [71, 72]. In cancer, persistent inflammation fuels genetic instability, tumour initiation, and progression through a network of inflammatory mediators and transcriptional regulators [73]. The convergence of these inflammatory pathways suggests a mechanistic interplay between the two diseases, where chronic low-grade inflammation in diabetes may contribute to tumorigenesis, while inflammation-driven cancers may reciprocally alter metabolic pathways. Two major cytokines, tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), play important roles in linking metabolic dysfunction to oncogenesis, acting as key molecular mediators that sustain inflammatory signalling in both conditions (Figure 8). TNF-α is a potent pro-inflammatory cytokine predominantly secreted by macrophages, adipocytes, and vascular endothelial cells, with widespread effects on metabolic and cancer-related processes [74, 75]. In diabetes, TNF-α contributes to insulin resistance by interfering with insulin receptor signalling through the serine phosphorylation of insulin receptor substrate-1 (IRS-1), which inhibits insulin-mediated glucose uptake and exacerbates hyperglycaemia [76]. Additionally, TNF-α promotes lipolysis, leading to increased levels of free fatty acids (FFAs), which further disrupt insulin sensitivity by activating inflammatory pathways in muscle and liver tissues [77]. These metabolic disturbances create a state of chronic, systemic inflammation that predisposes diabetic patients to complications, including endothelial dysfunction and increased susceptibility to malignancies.

In addition to its involvement in diabetes, TNF-α is acknowledged as a contributor to tumorigenesis due to its regulatory influence on critical oncogenic signalling pathways. Chronic TNF-α signalling has been demonstrated to activate nuclear factor-kappa B (NF-κB), a transcription factor that regulates the expression of genes associated with cellular survival, proliferation, and inflammatory responses [78, 79]. This persistent activation leads to an environment conducive to tumour initiation and progression, particularly through mechanisms such as ROS and RNS generation, which induce DNA damage and genetic instability [80]. Furthermore, TNF-α stimulates the

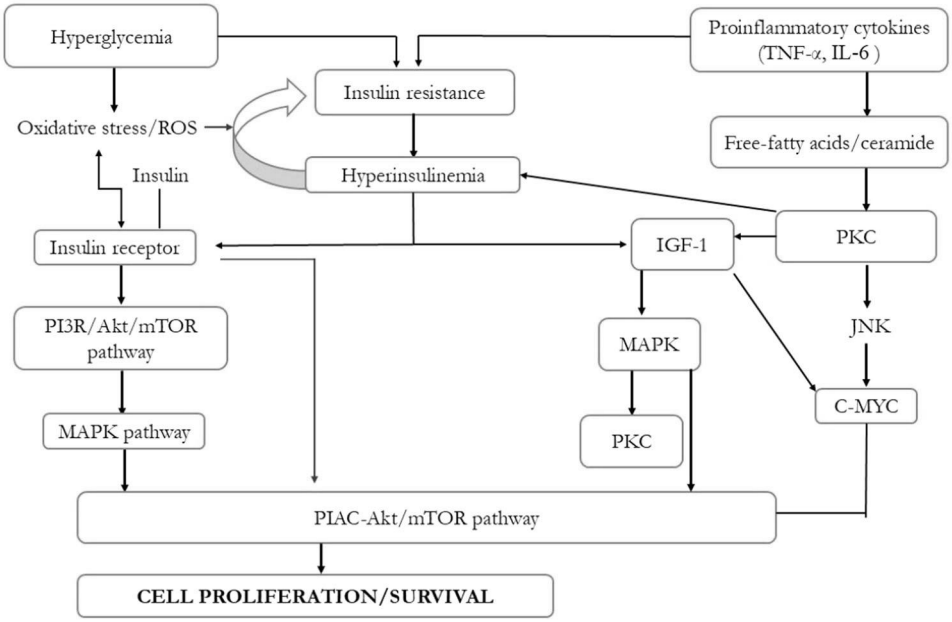

FIGURE 8 | Interlinked molecular mechanisms between diabetes and cancer (*the interplay of hyperglycaemia, insulin resistance, inflammation, and oxidative stress activates key signalling pathways (PI3K/Akt/mTOR, MAPK, PKC) that drives cell proliferation and survival. IGF-1 links insulin signalling to these effects*).

secretion of vascular endothelial growth factor (VEGF), thereby promoting angiogenesis which is an essential process for tumour development and metastatic progression [81]. Studies have also demonstrated that long-term TNF-α exposure can induce a cancer stem cell phenotype, as seen in oral squamous cell carcinoma, where TNF-α increased tumour-forming sphere ability and upregulated stem cell markers [82, 83].

Similarly, IL-6 plays an integral role in orchestrating the inflammatory response in both diabetes and cancer. Elevated circulating levels of IL-6 are frequently observed in diabetic patients, where it has been implicated in β-cell dysfunction, insulin resistance, and hepatic glucose overproduction [84, 85]. IL-6 impairs insulin receptor signalling by inducing the expression of suppressor of cytokine signalling 3 (SOCS3), a negative regulator that attenuates the activity of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), thereby contributing to reduced insulin sensitivity and metabolic dysfunction [86, 87]. This pro-inflammatory cytokine also influences adipose tissue metabolism, contributing to obesity-associated insulin resistance by altering adipokine secretion and increasing lipolysis [88].

In cancer, IL-6 exerts profound oncogenic effects, primarily through activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [89]. Upon binding to its receptor IL-6Rα and co-receptor gp130, IL-6 triggers the phosphorylation of JAK kinases, leading to the activation of STAT3, a transcription factor that drives cancer cell proliferation, survival, and immune evasion [89, 90]. This signalling cascade has been identified as a key regulator of cancer stem cell maintenance, promoting the expression of pluripotency-related genes such as Sox2, Nanog, and Oct4, which sustain the proliferation and tumorigenic potential of malignant cells [91]. Furthermore, IL-6 has been implicated in epigenetic modifications that promote tumorigenesis, including hypermethylation of tumour suppressor genes and hypomethylation of long interspersed nuclear element-1 (LINE-1), leading to increased genome instability and cancer progression [92].

Several synthetic curcumin derivatives achieve their therapeutic effects by suppressing these key inflammatory mediators. For example, the nitro-substituted analogue (Compound **4**) reduces TNF-α and IL-6 levels under hyperglycaemic conditions [44], while methoxylated derivatives such as Compound **24** selectively degrade ARs and downregulate NF-κB signalling in prostate cancer models [59, 60]. Likewise, BDMC33, another curcumin derivative, demonstrated significant anti-inflammatory effects by suppressing NF-κB and MAPK signalling pathways in macrophages, resulting in a marked reduction in TNF-α and IL-1β secretion and attenuating LPS-induced inflammatory responses [93]. Beyond NF-κB modulation, curcumin analogues FLLL32 and FLLL62 demonstrated anticancer activity by selectively inhibiting STAT3 phosphorylation, thereby inducing apoptosis in renal cell carcinoma and melanoma cells. This mechanism is further complemented by the suppression of VEGF secretion, thereby limiting tumour angiogenesis [94]. In pancreatic cancer models, the curcumin analogue, C66, was shown to inhibit JNK-mediated inflammation, leading to a significant reduction in the expression of pro-inflammatory cytokines, including IL-1β, IL-6, and IL-8, thereby attenuating tumour progression [91]. Similarly, C66 exerted renoprotective and cardioprotective effects in diabetic models by activating Nrf2 and inhibiting JNK signalling, effectively reducing fibrosis, oxidative stress, and inflammation [95]. Additionally, the thiazolyl hydrazone curcumin analogue, RI75, demonstrated strong anti-inflammatory activity through the inhibition of TNF-α and IL-6 production, alongside notable analgesic and anti-oedematogenic effects in vivo [96]. In metabolic disorders, curcumin analogues L2H21 and L50H46 have been shown to mitigate oxidative stress and inflammation in diabetic models by restoring endothelial homeostasis through the

normalisation of IL-6, TNF-α, and extracellular matrix protein expression, thereby reducing the risk of diabetes-associated complications such as nephropathy and cardiomyopathy [97]. Furthermore, L6H4, a novel curcumin analogue, has been found to alleviate liver fibrosis and insulin resistance in diabetic rats through the downregulation of TGF-β1 and TIMP-2 while restoring MMP-2 expression, leading to improved hepatic and metabolic function [98]. These findings illustrate how targeted structural modifications can extend curcumin's anti-inflammatory potential into disease-specific contexts.

6.2 | Oxidative Stress

Oxidative stress, whether arising from hyperglycaemia in diabetes or from mitochondrial dysfunction in cancer, represents another shared mechanism that synthetic curcumin derivatives can effectively modulate. Oxidative stress is a state of physiological imbalance in which ROS and free radicals exceed the neutralising capacity of the body's antioxidant defence system [99]. It is primarily driven by mitochondrial oxidative phosphorylation and other endogenous metabolic reactions [100]. While low levels of ROS are involved in normal cellular signalling and immune defence, their excessive accumulation leads to oxidative damage to critical biomolecules, including lipids, carbohydrates, proteins, and DNA [101, 102]. Scientific evidence supports the hypothesis that oxidative stress serves as a pivotal link between diabetes and cancer, highlighting a shared pathological mechanism that underlies both diseases. Diabetic patients exhibit chronically elevated levels of ROS due to persistent hyperglycaemia and metabolic dysfunction. This oxidative burden, combined with impaired antioxidant defences, heightens susceptibility to DNA damage, genetic mutations, and oncogenic transformation. The excessive ROS generated in diabetes not only accelerates cellular aging and dysfunction but also fuels chronic inflammation, which is a well-established driver of tumorigenesis [103]. These overlapping pathways suggest that diabetes and cancer are interconnected through a network of oxidative stress-induced molecular alterations, which collectively promote cellular dysfunction, immune dysregulation, and malignant transformation. One of the key mechanisms by which diabetes-associated oxidative stress fosters cancer development is insulin resistance and hyperinsulinemia (Figure 8). In Type 2 diabetes, insulin resistance forces pancreatic β-cells to secrete excessive insulin to compensate for reduced glucose uptake. This compensatory hyperinsulinemia stimulates the insulin-like growth factor (IGF) pathway (Figure 8), which plays a crucial role in cell proliferation, differentiation, and survival [103, 104]. IGF signalling promotes not only mitogenic and anti-apoptotic pathways but also actively contributes to the induction of epithelial-to-mesenchymal transition (EMT), a pivotal mechanism underlying cancer metastasis. By promoting unchecked cell growth and inhibiting programmed cell death, hyperinsulinemia creates an environment that is highly conducive to tumour initiation and progression. Another major contributor to the diabetes–cancer link is mitochondrial dysfunction, which disrupts cellular energy metabolism and compromises genomic stability. In diabetes, chronic hyperglycaemia and oxidative stress impair mitochondrial function, leading to inefficient ATP production and increased ROS generation. This dysregulation damages mitochondrial DNA (mtDNA), impairing key components of oxidative phosphorylation and further exacerbating ROS accumulation [105, 106]. The resulting oxidative damage to nuclear and mtDNA heightens the risk of oncogenic mutations, thereby increasing the likelihood of cancerous transformation. Furthermore, mitochondrial dysfunction in diabetes compromises DNA repair mechanisms, making cells more vulnerable to genotoxic stress and malignant transformation. In diabetes, the compromised antioxidant defence system exacerbates oxidative stress and its deleterious impact on cellular homeostasis. Under physiological conditions, antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase play a crucial role in neutralising excessive ROS, thereby mitigating oxidative damage. However, diabetic conditions are characterised by a marked reduction in the activity of these enzymes, resulting in a disrupted balance between ROS generation and their elimination [107]. This heightened oxidative stress state creates a self-perpetuating cycle in which excessive ROS levels cause further depletion of antioxidant reserves, increasing the susceptibility of DNA, proteins, and lipids to oxidative damage. Such oxidative insults not only accelerate diabetic complications but also serve as a prelude to oncogenic transformation by fostering genetic instability and aberrant cell signalling.

Several studies have highlighted the promising therapeutic potential of curcumin derivatives in both cancer and diabetes treatment, primarily through their ability to modulate ROS and influence key cellular pathways. Curcumin derivatives that increase electrophilic reactivity, such as chalcone conjugates (Compounds **26** and **27**) [62] and metal-curcumin complexes (Compound **28**) [63], demonstrate the ability to amplify oxidative stress selectively in tumour cells, whereas methoxylated analogues like Compound **24** [59, 60] provide antioxidant protection in hyperglycaemia-induced oxidative injury. Olender et al. [62] and Nakamae et al. [108] demonstrated that curcumin derivatives significantly upregulated ROS levels, leading to tumour suppression without noticeable side effects, highlighting the role of ROS modulation as a potential mechanism underlying anticancer effects. Similarly, Zheng et al. [109] and Liang et al. [110] explored novel curcumin analogues B63 and MC37, respectively, both of which induced mitochondrial dysfunction, disrupted the cell cycle, and triggered apoptosis through ROS-mediated mechanisms, showcasing their enhanced anticancer potential compared to native curcumin. Abdel Aziz et al. [49] also investigated the effects of a water-soluble curcumin derivative (**NCD**) in a model of type 1 diabetes and reported a reduction in oxidative stress markers, potentially mediated through the induction of heme oxygenase-1 (HO-1). These research outcomes underscore the versatility of curcumin derivatives in redox modulation across different disease conditions such as cancer and diabetes.

6.3 | The PI3K/Akt/mTOR Pathway

Dysregulation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signalling cascade is central to both insulin resistance and

oncogenic transformation, making it a critical target for several synthetic curcumin derivatives. This evolutionarily conserved pathway operates downstream of receptor tyrosine kinases such as the insulin and insulin-like growth factor-1 (IGF-1) receptors, positioning it as a vital mediator of cellular metabolism, proliferation, and survival [111]. In glucose homeostasis, insulin binding to its receptor initiates a signalling cascade involving phosphorylation of insulin receptor substrates (IRSs), recruitment of PI3K, and subsequent activation of Akt (Figure 8). This pathway promotes glucose uptake and glycogen synthesis. However, in Type 2 diabetes mellitus (T2DM), insulin resistance impairs this signalling pathway, leading to disrupted glucose metabolism and reduced insulin sensitivity [112]. Conversely, in cancer, the same pathway is often hyperactivated, primarily due to genetic alterations such as mutations in PIK3CA, Akt isoforms, or loss of PTEN. This persistent activation supports malignant transformation by promoting uncontrolled cell growth, survival, and metabolic reprogramming [113]. Notably, Akt enhances glycolysis and inhibits apoptotic signalling, enabling cancer cells to evade cell death [114, 115]. mTOR, acting downstream of Akt, forms two functional complexes: mTORC1 and mTORC2. mTORC1 responds to growth signals and promotes anabolic processes such as protein and lipid synthesis through targets like S6 kinase and 4E-BP1. In T2DM, chronic mTORC1 activation contributes to insulin resistance by triggering serine phosphorylation of IRS proteins, thereby impairing insulin signalling [116, 117]. In cancer, mTORC1 facilitates tumour growth by enhancing glycolysis, lipid biosynthesis, and angiogenesis [118, 119]. It also upregulates HIF-1α and hexokinase 2 (HK2), thereby sustaining the Warburg effect and fuelling tumour cell proliferation [120–122]. Meanwhile, mTORC2 supports cytoskeletal organisation and completes Akt activation via phosphorylation at Ser473, further amplifying survival signals in cancer cells. Unlike mTORC1, mTORC2 is not acutely sensitive to rapamycin, which complicates targeted therapies and may paradoxically enhance Akt signalling through feedback loops [123–126].

The PI3K/Akt/mTOR pathway also orchestrates lipid metabolism in both conditions. In diabetes, insulin resistance promotes lipogenesis via activation of SREBP1c and PPARγ, contributing to lipotoxicity and inflammation [127]. Similarly, in cancer, elevated lipid biosynthesis supports rapid proliferation and membrane production, driven by mTORC1-mediated activation of SREBP1c and suppression of FOXO1 by Akt [128–130]. Apoptotic regulation is another shared feature between diabetes and cancer. While β-cell apoptosis contributes to T2DM progression, cancer cells evade apoptosis via Akt-mediated inhibition of pro-apoptotic factors such as BAD, BIM, and caspase-9 [131]. Additionally, Akt-driven activation of MDM2 promotes degradation of p53, further enhancing cell survival [132]. Altogether, the PI3K/Akt/mTOR pathway serves as a molecular bridge linking the dysregulated metabolism of diabetes with the proliferative and survival mechanisms of cancer, highlighting its potential as a therapeutic target in both diseases.

Emerging studies have explored the therapeutic modulation of this pathway using natural product derivatives. Notably, synthetic curcumin analogues have shown promise in targeting key nodes of the PI3K/Akt/mTOR axis. For instance, Abdel Aziz et al. [49] demonstrated that a water-soluble curcumin derivative (**NCD**) reduced oxidative stress and modulated HO-1 expression in a diabetic model, indirectly influencing Akt signalling. Compound **3** improved insulin sensitivity through IRS-1/GLUT-4 activation [43], while Chen et al. [44] demonstrated that Compound **4** alleviated hyperglycaemia-induced inflammation and fibrosis in diabetic mice via inhibition of the P38 and Akt pathways, further supporting the role of curcumin analogues in the management of diabetic complications. Also, phosphorylated curcumin derivatives, Compound **25** [61], and nitrooxy-curcumin (Compound **30**) [65] inhibited survival signalling in cancer models. These findings underscore the potential of curcumin-based therapeutics to concurrently mitigate hyperglycaemic damage and tumorigenic signalling, positioning the PI3K/Akt/mTOR pathway as a viable intervention point for dual disease management.

Overall, the collective evidence indicates that rational structural optimisation of curcumin through modifications such as methoxylation, halogenation, heterocyclic fusion, or polar conjugation directly supports its ability to suppress inflammation, restore redox balance, and modulate PI3K/Akt/mTOR signalling. These mechanistic effects explain their dual efficacy across diabetes and cancer, two diseases driven by overlapping oxidative and inflammatory pathways. These overlaps not only strengthen the therapeutic argument for synthetic derivatives of curcumin but also illustrate how rational design involving functional group modifications of curcumin can simultaneously address these two diseases linked by common molecular pathways.

7 | Conclusion and Future Directions

Curcumin derivatives continue to attract strong research interest because they offer promising strategies to overcome the pharmacokinetic and pharmacodynamic limitations of native curcumin. As this review has outlined, structural modifications such as methoxylation, halogenation, phosphorylation, hybridisation, and metal complexation have produced derivatives with improved solubility, stability, metabolic resistance, and target selectivity. These advances have expanded the therapeutic spectrum of curcumin derivatives into both diabetes and cancer, two diseases that share interconnected mechanisms, including chronic inflammation, oxidative stress, and dysregulated signalling. However, the limitations of the reviewed derivatives, as highlighted in Table 3 and discussed in Section 5.1 indicate that significant challenges remain before clinical translation can be realised. Many derivatives have demonstrated activity primarily in vitro, with limited or no in vivo validation. Others show strong preclinical efficacy but lack long-term safety data. Prodrug strategies such as phosphorylation offer potency advantages but introduce pharmacokinetic complexity that may complicate dosing. These limitations should shape future research on synthetic curcumin derivatives in several ways. Primarily, rigorous in vivo studies and early-phase pharmacokinetic profiling are essential to confirm bioavailability, tissue distribution, and safety. Additionally, translational efforts should integrate systems biology and computational modelling to predict off-target effects and optimise structural modifications. Furthermore, exploring the synergistic effects of curcumin derivatives with existing therapies and consideration of advanced drug delivery systems like liposomes and nanoencapsulation may lead to improved outcomes while reducing adverse effects. More in-depth mechanistic studies are also required to further understand the molecular pathways involved, which

could lead to the development of more specific treatments. There is also potential for personalised medicine approaches, tailoring curcumin derivative-based therapies to individual genetic and metabolic profiles, particularly for complex diseases like diabetes and cancer. Ultimately, the future of curcumin derivatives lies not only in designing more potent analogues but in translating these innovations into safe, effective therapies that address the intertwined burden of diabetes and cancer.

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Ethics Statement

The article does not require ethical approval as it is a review article.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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