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REVIEW

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Co-administration of curcumin with other phytochemicals improves anticancer activity by regulating multiple molecular targets

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Abstract

Natural plant phytochemicals are effective against different types of diseases, including cancer. Curcumin, a powerful herbal polyphenol, exerts inhibitory effects on cancer cell proliferation, angiogenesis, invasion, and metastasis through interaction with different molecular targets. However, the clinical use of curcumin is limited due to poor solubility in water and metabolism in the liver and intestine. The synergistic effects of curcumin with some phytochemicals such as resveratrol, quercetin, epigallocatechin-3-gallate, and piperine can improve its clinical efficacy in cancer treatment. The present review specifically focuses on anticancer mechanisms related to the co-administration of curcumin with other phytochemicals, including resveratrol, quercetin, epigallocatechin-3-gallate, and piperine. According to the molecular evidence, the phytochemical combinations exert synergistic effects on suppressing cell proliferation, reducing cellular invasion, and inducing apoptosis and cell cycle arrest. This review also emphasizes the significance of the co-delivery vehicles-based nanoparticles of such bioactive phytochemicals that could improve their bioavailability and reduce their systemic dose. Further high-quality studies are needed to firmly establish the clinical efficacy of the phytochemical combinations.

KEYWORDS
anticancer mechanisms, cancer, curcumin, phytochemical combinations, synergistic effects

1 | INTRODUCTION

Cancer is one of the main challenges in the field of health, which involves more than 14 million new cases with almost 8 million deaths annually (Torre et al., 2015). Cell resistance to chemotherapy or radiotherapy is associated with increased mortality (Kawasaki et al., 2008). Therefore, it is essential to expand an effective alternative strategy to manage and promote the healing process of cancer. Phytochemicals as bioactive molecules present in a plant-based diet. They have been related to the protection from and/or treatment of different chronic diseases such as cancer (Surh, 2003). Different preclinical and clinical studies demonstrated that phytochemicals could modulate several signaling pathways participating in cancer progression and development.

Cancer chemoprevention is narrated as a new method to suppress or inverse the process of cancer using synthetic or natural compounds. Recently, chemopreventive conception has been extended to target all stages of the cancer process, including cancer initiation and progression (Greenwald, 2002). Phytochemicals from herbs have emerged as a new source of cancer chemoprevention, and as an adjuvant to chemotherapy drugs; thus, many researchers have shown increased attention in this field. These components can prevent

cancer initiation and progression through DNA damage, free-radical scavenging, and apoptosis (Greenwald, 2002). In addition to the anti-inflammatory and antioxidant properties of some phytochemicals as a chemopreventive agent, phytochemical utilization suppressed different cell signaling pathways related to the progression of cancer cells and preserved normal cells against chemotherapy-induced side effects in various clinical trials (Jain et al., 2021).

The co-administration of two or more therapeutic agents with synergistic biological effects is commonly utilized to prevent or treatment of chronic diseases such as cancer. Different studies have represented that the combination of herbal substances can elevate their anticancer effects (Guan et al., 2020; Maasomi et al., 2017). Curcumin, a phytochemical extracted from the rhizome of turmeric (*Curcuma longa* L.), regulates different molecular targets which are required for the treatment of most diseases, such as cancer (Goel et al., 2008). The main disadvantage of curcumin is its low bioavailability and poor absorption (Rai et al., 2015). Different studies indicate improved anticancer efficacy of co-administrated curcumin with other phytochemicals (Sayyed et al., 2022; K. Wang et al., 2016). In addition, the encapsulation of phytochemicals in nanoparticle delivery systems has been promising in their delivery process. Nanoparticle delivery of phytochemicals has been demonstrated to improve their solubility and modify unfavorable pharmacokinetic parameters (Xie et al., 2016).

In this review, we will focus on the co-administration of curcumin with some potent anticancer phytochemicals as well as their target effectors in cancers.

2 | POTENTIAL THERAPEUTIC STRATEGIES OF PHYTOCHEMICALS

Interaction of two or more therapeutic phytochemicals has different effects on each other, including the promotion of phytochemical potency through molecular interaction with adjuvant substance (potentiation), combined efficacy equivalent to the sum of individual effects (additive), combined efficacy greater than the sum of individual effects (synergistic), and combined efficacy less than the sum of individual effects (Lila & Raskin, 2005; Pöch, 1993).

A combination of two or more phytochemicals demonstrates synergistic effects in cells through five mechanisms: (1) increase the bioavailability of phytochemicals; (2) enhance antioxidant capacity; (3) target same or different signaling pathways; (4) effects on gut microbiome such as reduce endotoxin, increase gut integrity and change microbial profiles; and (5) exert two or more of these four mechanisms simultaneously (L. Zhang, Virgous, et al., 2019).

Recently, more studies have been conducted on the effectiveness of phytochemical combinations in cancer. Hence, in this review, we considered studies that investigated the combined effects of curcumin with some of the most important phytochemicals on cancers, either in their free form or co-encapsulated by drug delivery systems.

3 | THE ANTICANCER EFFICACY OF SINGLE POLYPHENOLS PLUS THEIR COMBINATION WITH CURCUMIN

3.1 | Curcumin, resveratrol, and curcumin–resveratrol combination

Curcumin, a natural polyphenol, is extracted from the rhizome of *C. longa* and applied in the pharmacological industry as an anticancer ingredient (Yallapu et al., 2014). Anticancer activity of curcumin has been demonstrated in several cancers, such as breast (Inano & Onoda, 2002), cervical (Aedo-Aguilera et al., 2019), and lung cancers (L. Zhang, Tao, et al., 2019).

Anticancer effects of curcumin on biological pathways have been revealed in oncogene expression, cell cycle regulation, mutagenesis, apoptosis, tumorigenesis, and metastasis. Curcumin has exerted an antiproliferative effect in various cancers and is a suppressor of the transcription factor nuclear factor kappa (NF-κB) and NF-κB regulated gene products that participate in tumor growth and carcinogenesis, including cyclin D1, vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), c-myc, Bcl-2, ICAM-1, and matrix metalloproteinase-9 (MMP-9) (Wilken et al., 2011). Curcumin can impair epithelial to mesenchymal transition (EMT), as an important process in cancer metastasis, by down-regulating the expression E-cadherin, N-cadherin, β-catenin, Slug, AXL, Twist1, Vimentin, and fibronectin protein expression in cancer cells thereby repressing invasion and migration capability (Gallardo & Calaf, 2016). Curcumin has been indicated to suppress the multidrug resistance-related ATP binding cassette transporter, ABCG2 (Shukla et al., 2009). In addition, curcumin can minimize the unpleasant side effects related to chemotherapeutic drugs (Panda et al., 2017).

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene), a non-flavonoid polyphenol, occurs in plenty of species of plants, including grapes, peanuts, pines, and berries (Cucciolla et al., 2007). The anticancer efficacy of resveratrol has been shown against many cancers, such as hepatic, pancreatic, postmenopausal breast, prostate, colorectal (Carter et al., 2014), and lung cancer (Yousef et al., 2017). Resveratrol can modulate transcription factor NF-κB, cyclooxygenase activity, and suppress cytochrome P450 isoenzyme (CYP A1) drug metabolism. In addition, resveratrol may affect TP53, FAS/FAS-ligand mediated apoptosis, and mechanistic target of rapamycin (mTOR) activity (Diaz-Gerevini et al., 2016).

A combination of curcumin and resveratrol has shown significant potential in combating various cancers, as reported in multiple studies.

Different studies have reported desired efficacy of this combination on lung carcinogenesis.

It has been reported that these phytochemicals, in combination with together, can induce apoptosis through the activation of caspase 3, caspase 9, and P53 against lung carcinogenesis (Malhotra et al., 2014). Co-administration with curcumin and resveratrol to benzo(a)pyrene-treated mice resulted in an advancement in the antioxidant enzyme activities of superoxide dismutase and glutathione-S-

transferase and an appreciable decrease in the drug-metabolizing enzymes (cytochrome b5 and P450) to prevent lung carcinogenesis (Y. Liu, Wu, Yu, et al., 2015). Phytochemicals probably preserve normal zinc levels for the optimized functioning of the superoxide dismutase against oxidative stress (Y. Liu, Wu, Yu, et al., 2015). Moreover, Malhotra et al. have shown that combined treatment with curcumin and resveratrol to benzo(a)pyrene-treated mice caused an improvement in the zinc levels, regulation of inflammatory enzyme activity of Cox-2 and protein expression of p21 (Malhotra et al., 2011).

As an efficacy on various cancers, a recent study has shown that this combination affects a stronger cytotoxic effect than individual treatment on breast and salivary gland cancers. The combined treatment induces more apoptotic cell death in these cells than individual treatment by the appearance of the cleaved form of poly (ADP-ribose) polymerase (PARP). In addition, it has been reported that co-administration with curcumin and resveratrol dysregulated the PI3K/AKT/mTOR pathway, autophagy, intracellular reactive oxygen species (ROS), endoplasmic reticulum (ER) stress/unfolded protein response (UPR) and up-regulated of pro-death UPR molecule CHOP in cancer cell lines. Thereby, these compounds reduced cancer cell survival and exerted a greater cytotoxic effect (Arena et al., 2021). A recent study has shown that this combination can inhibit chemoresistance in epithelial ovarian cancer cells by inhibiting the PI3K/AKT/mTOR pathway (Muhanmode et al., 2021).

It has been reported that co-administration of these phytochemicals can be modulated prostate carcinogenesis. In this study, combined treatment with curcumin and resveratrol to 3,2′-dimethyl-4-amino biphenyl treated animals indicated a considerable decrease in lipid peroxidation, ^{3}H-thymidine uptake, ^{14}C glucose uptakes/turnover with significant modulation in biochemical indices, including drug-metabolizing and antioxidant enzymes. In this regard, this finding implies that the combination affects biochemical and biophysical modulators in prostate carcinogenesis (Guo et al., 2020). In a further study focused on antitumor progression outcomes, it was demonstrated that these compounds had down-regulative effects on activated p-Akt (a serine/threonine kinase), cyclin D1, mTOR, and androgen receptor in an animal model for prostate cancer with loss of phosphatase and tensin homolog (PTEN) (Narayanan et al., 2009). Furthermore, curcumin and resveratrol compound have therapeutic potential in colorectal cancer cell lines (DLD-1 and Caco-2) with an additive efficacy for the Caco-2 cell line and a synergistic efficacy for the DLD-1 cell line. The combined phytochemicals target multiple genes related to the modulation of apoptosis, including PMAIP1, ZMAT3, BID, CASP3, CASP7, and FAS (Gavrilas et al., 2019). This compound debilitates NF-κB activity, the constitutive activation of epidermal growth factor receptor (EGFR), its family members, and insulin-like growth factor-1 receptor (IGF-1R) that elevate growth, angiogenesis, and metastasis in colon cancer (Majumdar et al., 2009).

Curcumin and resveratrol combination also exerts a synergistic antiproliferative effect on hepatocellular carcinoma Hepa1-6 cells. This combinatory treatment considerably activated caspase-3, -8, and -9, indicating apoptosis occurred more via the combinatory treatment than either agent alone. In addition, the expression of XIAP and survivin antiapoptotic proteins significantly down-regulated and ROS expression up-regulated in Hepa1-6 cells compared to the following treatment with either agent alone. Indeed, excess ROS increases cell death (Q. Du et al., 2013).

In another study, the antitumoral performance of curcumin and resveratrol combination has been indicated in head and neck carcinomas through an increase in the Bax/Bcl-2 ratio, the PARP-1 cleavage, the inhibition of phospho-extracellular signal-regulated kinase 1/2 (p-ERK1/2) (as pro-survival signaling proteins) simultaneously with the organization of autophagic vacuoles, an increase in the percentage of apoptotic sub-G1 cells and a decrease in the percentage of G0/G1 and G2/M cells compared to administered curcumin or resveratrol alone at the higher dose (Masuelli et al., 2014). Jaisamut et al. studied the anticancer efficacy of this compound in the form of a self-micro emulsifying formulation for co-delivery and improved water-solubility of curcumin and resveratrol. They reported that co-delivery treatment of curcumin and resveratrol organized in a self-microemulsifying formulation resulted in higher antioxidant activity and higher inhibition in colon cancer than applying each agent alone in the formulation (Jaisamut et al., 2017). Table 1 summarizes the in vitro and in vivo studies investigating the anticancer effects of the combination of curcumin and resveratrol.

Co-delivery vehicles-based nanoparticles for phytochemicals such as curcumin and resveratrol can improve their poor bioactivity and bioavailability.

It has been reported that co-nanoencapsulation of these phytochemicals in lipid-core nanocapsules enhances their photostability and antioxidant activity. Thus, nanoencapsulation of this compound can be useful in treating diseases associated with oxidative stress (Coradini et al., 2014). Moreover, the co-delivery of curcumin and resveratrol in polymeric micelles improves their solubility significantly (Carlson et al., 2014). A study reported by Huang et al. has shown that co-delivery liposome for loading curcumin and resveratrol exhibits more capability during preparation, heating, surfactant shock, and storage than those loaded with single polyphenol. In addition, co-encapsulation of this compound demonstrated the highest 2,2-diphenyl-1-picrylhydrazyl scavenging, inhibiting lipid peroxidation capacity and reducing power due to the improved dispersion and water solubility of polyphenols (Huang et al., 2019). In addition, recently, it has been shown that the curcumin–zein–resveratrol–chitosan nanocomplexes can improve the thermal stability, storage stability, physical stability, and photostability of encapsulated phytochemicals (S. Chen et al., 2020). In a recent study, Palliyage et al. have designated solid lipid nanoparticles (SLNs) loaded delivery vehicles for evaluating anticancer efficacy and skin penetration of a combination of these polyphenols. In the skin binding study, curcumin–resveratrol SLNs attachment locally to the skin was estimated to be more than 70%, indicating the efficacy of the loaded phytochemicals in treating localized melanoma. In addition, they reported that curcumin–resveratrol SLNs and curcumin–resveratrol solution had a strong synergistic inhibition in SK-MEL-28 melanoma cell proliferation (Palliyage et al., 2021). In another recent study related to nanoformulation, hepatocellular carcinoma-targeted nanoparticles with curcumin and

TABLE 1 In vivo and in vitro cancer studies related to the curcumin–resveratrol combination.

Type of study (cancer cells, animal)	Type of drug administration	Cancer	Findings	References
Cancer cells	Curcumin–resveratrol	Breast and salivary cancer	Reduces cancer cell survival and exerts a stronger cytotoxic effect by the combination	Arena et al. (2021)
Cancer cells	Curcumin–resveratrol	Colorectal cancer	Targets pro-apoptotic genes	Gavrilas et al. (2019)
Cancer cells	Curcumin–resveratrol	Hepatocellular carcinoma	Exhibits synergistic anticancer effects	Q. Du et al. (2013)
Animal/cancer cells	Curcumin–resveratrol	Colorectal cancer	Exhibits strong anticancer efficacy attributed to the suppression of proliferation and stimulation of apoptosis	Majumdar et al. (2009)
Animal/cancer cells	Curcumin–resveratrol	Prostate cancer	Alleviates prostate cancer occurrence due to the loss of the tumor suppressor gene PTEN	Narayanan et al. (2009)
Animal/cancer cells	Curcumin–resveratrol	Head and neck squamous cell carcinomas	The combined phytochemicals exhibited more effectiveness in suppressing in vivo and in vitro cancer growth compared with curcumin alone	Masuelli et al. (2014)
Animal	Curcumin–resveratrol	Prostate carcinogenesis	Modulates drug-metabolizing and antioxidant enzymes modulate biophysical indices such as a decrease in the ^{3}H-thymidine and ^{14}C glucose uptakes	Guo et al., 2020))
Animal	Curcumin–resveratrol	Lung carcinogenesis	Modulates p53 hyperphosphorylation, induces apoptosis and antioxidant enzyme activities, decreases drug-metabolizing enzymes, maintains appreciable zinc level to regulate COX-2 and p21 during the induction of lung carcinogenesis	Malhotra et al. (2014); Liu, Wu and Zhang (2015); Malhotra et al. (2011).

resveratrol were designated for improving the phytochemical properties of hepatocellular carcinoma. These polymeric nanoparticles led to a considerable reduction in the phytochemicals dosage, sustained phytochemicals release, enhanced the bioavailability of the loaded phytochemicals, and increased the concentration of the phytochemicals at the tumor target site (Zheng et al., 2022). Recently, Kou et al. have shown that compound of curcumin and resveratrol in nanosized dimension indicated synergistic anticancer efficacy on colon cancer by inducing cell cycle arrest, necrosis, and apoptosis in vitro and in vivo. Moreover, they reported that the combination of curcumin and resveratrol with modulated electro-hyperthermia significantly induced chaperone Hsp70 protein and inhibited tumor growth in BALB/c mice (Kuo et al., 2020). Thus, this combination indicates potent inhibitory effects on various cancers by targeting different molecules related to the proliferation and apoptosis signaling pathways. In addition, encapsulation of curcumin and resveratrol in co-delivery systems can improve their efficacy, but the evaluation of molecular factors in this field is almost neglected.

3.2 | Epigallocatechin-3-gallate and curcumin–epigallocatechin-3-gallate combination

Epigallocatechin-3-gallate, a green tea-extracted polyphenol, has been widely investigated for its anticancer and chemopreventive effects (Rady et al., 2018). Epigallocatechin-3-gallate has been found to depict the antiproliferation and apoptosis in colon cancer cells via modulation of AMP-activated protein kinase (AMPK) followed by the reduction in COX-2 expression (G. J. Du et al., 2012; Hwang et al., 2007). Apoptotic induction was also confirmed in non-small cell lung cancer (A549) cells in a p53-dependent pathway upon epigallocatechin-3-gallate treatment (Yamauchi et al., 2009). Epigallocatechin-3-gallate also moderated the process of EMT in various cancer types. Crosstalk of the ERK and Smad pathways has been indicated in the regulation of EMT (X. Chen et al., 2014; Mitra & Roy, 2017). Epigallocatechin-3-gallate repressed TGFβ-induced EMT via down-regulation of phosphorylated ERK and Smad2 in non-small cell lung cancer cells (L. C. Liu et al., 2012).

Epigallocatechin-3-gallate was shown to interact with MMP-2, -9, and extracellular matrix-degrading enzymes to facilitate invasion, thereby repressing invasion and metastasis in lung carcinoma (Negri et al., 2018). Epigallocatechin-3-gallate also down-regulated the expression of Oct-4, Nanog, and c-Myc, genes for maintaining pluripotency, thereby decreasing the spheroid forming potential of pancreatic and prostate cancer stem cells (S. N. Tang et al., 2010, 2012). Another anticancer effect of this photochemical was related to the suppressing drug efflux pumps of the cancer cells (W. Zhang, Zhang, et al., 2019).

A natural compound, including curcumin and epigallocatechin-3-gallate, demonstrates potential in growing anticancer therapy, but their clinical operation is commonly restricted by low tissue distribution and instability (Krupkova et al., 2016; Lopresti, 2018). Combined treatment of these phytochemicals can ameliorate the efficiency with synergistic effects.

A study by Jin et al. revealed that curcumin and epigallocatechin-3-gallate combination significantly debilitated tumor growth and angiogenesis in colorectal carcinoma. This compound had a more reducing effect on the mRNA levels of JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3) and IL-8 than each of them alone (Jin et al., 2017). Therefore, oncogenic signaling cascade and angiogenic promoter are inhibited through suppression of the JAK/STAT3/IL-8 signaling pathway. This combination also suppressed the cluster of differentiation 44 (CD44) positive breast cancer stem cells via modulating STAT3/NFκB signaling pathways. As a characteristic of cancer stem cells, tumor-sphere formation is potently inhibited under combined curcumin and epigallocatechin-3-gallate treatment compared to either treatment alone (Chung & Vadgama, 2015). It has been reported that this compound exerts a cytotoxicity effect synergistically toward breast cancer cells, and the animal study indicates a reducing effect on tumor growth. Moreover, the combined treatment exerted a more suppressive effect on the protein level of vascular endothelial growth factor receptor (VEGFR-1), as an angiogenic stimulating factor, than each of them alone (Somers-Edgar et al., 2008).

In another study, Wang et al. have shown combinatory effects of phytochemicals in combating resistant breast cancer. They reported that epigallocatechin-3-gallate might enhance the intracellular curcumin amount via modulating p-glycoprotein (P-gp) transporter function, which could potentially increase the cytotoxicity of curcumin in both doxorubicin-sensitive and resistant MCF-7 cells. In addition, the combinatory treatment has shown more effect on apoptotic rate than individual treatment. Moreover, evaluation of apoptosis-related proteins has shown a decreased effect on antiapoptotic protein Bcl-2 and surviving levels. In the following, the expression of caspase-7 and -9 down-regulated while the expression of cleaved caspase-7 and -9 up-regulated in both sensitive and resistant breast cancer cells after curcumin and epigallocatechin-3-gallate co-treatment (S. Wang et al., 2014).

The chemopreventive effects of curcumin and epigallocatechin-3-gallate combination were also investigated in non-small cell lung cancer (NSCLC). Cell cycle arrest of NSCLC happened at G1 and S/G2 phases, and cell cycle proteins cyclin B1 and cyclin D1 were suppressed significantly in the presence of this compound. In a lung cancer xenograft animal model, the combinatory treatment demonstrated a protective operation against the weight loss related to tumor burden. As another effect of this combined treatment, repression of cell growth and tumor growth was significantly indicated in NSCLC (Zhou et al., 2013). Previously, Ghosh et al. (2009) reported that simultaneous administration of curcumin and epigallocatechin-3-gallate exerted an antagonistic effect in chronic lymphocytic leukemia cells, but sequential administration of these phytochemicals increased cell death and could defeat stromal-mediated protection of cells. In another study, the advantageous anticancer effects of combined curcumin and EGCG were verified on PC3 prostate cancer cells. Antiproliferative effect of epigallocatechin-3-gallate improved on PC3 prostate cancer cells when it was combined with curcumin. The improved antiproliferative effect of epigallocatechin-3-gallate with curcumin was related to the up-regulation of the p21 protein synergistically, which resulted in prostate cancer cell growth arrest (Eom et al., 2015).

It has been shown that curcumin, epigallocatechin-3-gallate, and lovastatin combination has an inhibitory effect on esophageal cancer by suppressing cell growth, tumor growth, tumor cell invasion, and modulation of gene expressions such as p-Erk1/2, c-Jun, and COX-2.

Restoration of retinoic acid receptor-β_2 (RAR-β_2) expression inhibited esophageal cancer, and this can be provided with decreased expression of COX-2 and p-Erk1/2. The combinatory treatment inhibited COX-2 and p-Erk1/2 expression with induction of caspase-3 expression in esophageal cancer cells (Ye et al., 2012). In addition, combined treatment of curcumin and epigallocatechin-3-gallate has shown a synergistic effect in growth inhibition of normal, premalignant, and malignant oral cells (Khafif et al., 1998). Table 2 summarizes the in vitro and in vivo studies investigating the anticancer effects of the combination of curcumin and epigallocatechin-3-gallate.

In nanoformulation-based combination therapy, it has been shown that a dual targeting system with hyaluronic acid and fucoidan for the co-encapsulation of curcumin and epigallocatechin-3-gallate can improve their efficiency in prostate cancer therapy. The dual-targeted system was up-taken more into prostate cancer cells with a greater anticancer effect than the curcumin and epigallocatechin gallate combination solution (Chu et al., 2019). In a recent study, liposome synthesized from 1-palmitoyl-2-oleoyl-sn glycero-3-phosphocholine was utilized to increase the stability of the phytochemicals, which resulted in further increasing the stability of curcumin in co-embedded in the nano-liposome than curcumin encapsulated alone. The finding showed that the studied nanoformulation could be attended to for in vivo tests and used instead of dimethyl sulfoxide solvent in the in vitro tests (Piwowarczyk et al., 2022). Thus, targeted therapy based on liposomes could be a favorable vehicle to increase the concentration of related phytochemicals by careful delivery into cancer cells.

Co-encapsulation of curcumin and epigallocatechin-3-gallate also was assessed in zein-caseinate nanoparticles. Findings from the study indicated that epigallocatechin-3-gallate could be applied to enhance the functional features of curcumin-loaded nanoparticles, including its entrapment efficiency, bioaccessibility, and antioxidant activity (Yan et al., 2019). Moreover, in the presence of epigallocatechin-3-gallate, the efficacy of encapsulated curcumin was improved in the co-encapsulated phytochemicals/poly(N-vinylpyrrolidone) nanoparticles. For instance, the intestinal absorption of curcumin was enhanced due to the suppression of glucuronidation metabolic reaction by epigallocatechin-3-gallate with higher Caco-2 monolayer penetration (Y. Chen et al., 2022).

According to the investigated studies, this combination exerts anticancer effects on cancers by targeting the signaling pathways involved in proliferation, cell cycle, angiogenesis, drug resistance, and apoptosis. As we surveyed, more attention is needed to study these agents in co-encapsulated delivery systems with their related molecular mechanisms.

3.3 | Quercetin and curcumin–quercetin combination

Quercetin is a polyphenolic flavonoid ubiquitous in plant sources and it has therapeutic efficiency in the field of cancer prevention and cancer treatment. Quercetin derivatives exist in various fruits and vegetables, such as apples, red onions, olive oil, parsley, cocoa, tea, and citrus fruits, and it assigns about 60% of the total daily consumption of flavonoids (Harwood et al., 2007; Spagnuolo et al., 2012).

According to pharmacological studies, quercetin indicates antiinflammatory, antiproliferative, and anticancer effects (Rice-Evans

TABLE 2 In vivo and in vitro cancer studies related to the curcumin–epigallocatechin-3-gallate combination.

Type of study (cancer cells, animal)	Type of drug administration	Cancer	Findings	References
Cancer cells	Curcumin–epigallocatechin-3-gallate	Breast cancer	Reduces cancer stem cell phenotype via suppression of STAT3 and NFκB signaling pathways	Chung and Vadgama (2015)
Cancer cells	Curcumin–epigallocatechin-3-gallate	Breast cancer	Epigallocatechin-3-gallate increases the incorporation of curcumin in suppressing growth and inducing apoptosis of breast cancer resistance	S. Wang et al. (2014)
Cancer cells	Curcumin–epigallocatechin-3-gallate	Prostate cancer	Enhances synergistic inhibitory effect on PC3 cell proliferation	Eom et al. (2015)
Animal/cancer cells	Curcumin–epigallocatechin-3-gallate	Colorectal carcinoma	Exerts antiangiogenic effect by blocking JAK/STAT3/IL-8 signaling pathway	Jin et al. (2017)
Animal/cancer cells	Curcumin–epigallocatechin-3-gallate	Breast cancer	Exhibits cytotoxicity synergistically in ER alpha-breast cancer	Somers-Edgar et al. (2008)
Animal/cancer cell	Curcumin–epigallocatechin-3-gallate	Non-small cell lung cancer	Exerts synergistic antiproliferation effect, inhibits strong tumor growth	Zhou et al. (2013)

et al., 1996). Quercetin exerts anticancer effects on various cancers, including breast, cervical, gastric, and prostate cancer (Deng et al., 2013; Shang et al., 2018; Sundaram et al., 2019; Ward et al., 2018). Several mechanisms have represented favorable effects of quercetin on cancers. As an antioxidant agent, its antioxidant functionality is mostly exhibited by affecting glutathione, enzyme activity, ROS, and signal transduction paths (Xu et al., 2019). Quercetin activates the apoptosis pathway through caspase-3, -8, and -9 activation and induction of cytosolic Ca^{2+} release, followed by a decrease in mitochondrial membrane potential (MMP) (Chien et al., 2009). This phytochemical can be suppressed the cell cycle in different checkpoints such as G2/M, G1/S, and G1 (Jeong et al., 2009; Mu et al., 2007). As antiangiogenesis functionality in cancer, this phytochemical down-regulates the VEGFR-2-mediated angiogenesis protein as well as the downstream regulatory factor AKT (Balakrishnan et al., 2016). As antimetastatic functionality, quercetin can suppress the EMT by regulating E-cadherin and down-regulating Twist-1 expression in colorectal cancer cell lines (Feng et al., 2018). In addition, it can repress the level of MMP-2 and MMP-7 in pancreatic cancer, which is associated with the EMT process. Researchers also indicated that this phytochemical could suppress the invasion of pancreatic cancer by suppressing the STAT-3 signaling pathway and inverse the malignant progress induced by interleukin-6 (IL-6) (Yu et al., 2017). Different studies have exploited co-administrating curcumin and quercetin to enhance their efficacy. As an advantage of this combination, quercetin blocks the curcumin and albumin linkage, thereby enhancing the cellular uptake of curcumin (Kim et al., 2012). This combination can synergistically modulate breast cancer type 1 susceptibility protein (BRCA1) loss by increasing histone acetylation of the BRCA1 promoter. Loss of function of this tumor suppressor gene has been identified mostly in triple-negative breast cancer (TNBC). In addition, in comparison to their activity, it has been shown that curcumin and quercetin combination can considerably inhibit the EMT process by inhibiting MMP-9 expression that induces it (Alegría-Torres et al., 2011; Kundur et al., 2019). The combinatory treatment of these phytochemicals significantly inhibited gastric cancer cell proliferation and induced apoptosis via the mitochondrial pathway. This compound has exerted a stronger effect on apoptosis mediated by the mitochondrial pathway, including the collapse of mitochondrial membrane potential ($\Delta\Psi m$), cytochrome c release, and inhibited phosphorylation of AKT and ERK than curcumin and quercetin alone (J. Y. Zhang et al., 2015). Synergistic antiproliferative effect of curcumin and quercetin also has been indicated in A375 melanoma cells, and it has been reported that the phytochemicals exert down-regulative effects on Dishevelled 2 (Dvl2) and Axin proteins related to Wnt/β-catenin signaling path and its down-stream target genes, cyclin D1, and Cox2 (Srivastava & Srivastava, 2019). The Wnt/β-catenin pathway regulates the proliferation of cancer cells (Shtutman et al., 1999). In addition, the indexes of mitochondrial apoptotic pathway and ROS level significantly induced in chronic myeloid leukemia cancer cells (K562) treated with the combination, and their effective dose was reduced, followed by the prevention of side effects on normal cells (Altundağ et al., 2018).

In a recent study, also the synergistic effect of curcumin and quercetin combination has been investigated in K562 cells, and it has been reported that this compound has an effectual effect on genes, which exclusively associated with p53, NF-κB, and TGF-α signaling pathways. Various genes are affected by the combined phytochemicals, including BTG2 tumor suppressor, Fas, AKT, IFN-γ, and cell cycle regulators (CDKN1A; also known as p21 and CDKN1B; also known as p27). The combination has shown an up-regulative effect on mRNA and protein expressions of P21 and p27 cyclin-dependent kinase inhibitors (Altundağ et al., 2021). In prostate cancer, treatment with this compound indicated more effectiveness in suppressing cancer cell proliferation than individual treatment. It has been shown that the phyto-compound has more ability to inhibit DNA methyltransferase activity for re-sensitizing prostate cancer cells to antineoplastic agents than either curcumin or quercetin (Sharma et al., 2016). Anticarcinogenic properties of the combination are also indicated through its effect on antioxidant activity and drug-metabolizing enzymes against induced lung carcinogenesis (Y. Liu, Wu, & Zhang, 2015). In addition, it has been shown that the phytochemical combination exerts synergistic modulatory effects on p53 to ameliorate its tumor suppression function during lung carcinogenesis (P. Zhang & Zhang, 2018). Table 3 summarizes the in vitro and in vivo studies investigating the anticancer effects of the combination of curcumin and quercetin.

About the studies related to the co-nanodelivery system of this compound, a recent study has shown that co-encapsulation of curcumin and quercetin in an apoferritin nano vehicle can ameliorate their synergistic effect by increasing bio-availability and specific targeting of MCF7 breast cancer cells (Mansourizadeh et al., 2020). In addition, in MCF7 breast cancer cells, the co-encapsulated phytochemicals have shown significant efficacy in nanoemulsion vehicles (Rahman et al., 2022). In another nanoformulation study, it has been shown that curcumin and quercetin encapsulated polymeric nanoparticles demonstrate improved stability and enhanced anticancer functionality in multiple cancer cells than the free curcumin (Chidambaram & Krishnasamy, 2014). Thus, a combination of curcumin and quercetin can exert significant anticancer effects on different cancers by targeting various molecular pathways. In addition, investigation of other co-delivery systems for this combination can promote its anticancer efficacy.

3.4 | Piperine and curcumin–piperine combination

Piperine is a phenolic ingredient that has been extracted from plants of the Piperaceae family, such as long pepper (*Piper longum*) and black pepper (*Piper nigrum*) (Singh, 1992). Piperine represents different pharmacological properties, including antioxidant activity (Vijayakumar et al., 2004), chemopreventive effect, and cytotoxicity in cancer cells via inducing various effectors' proteins associated with apoptosis (Lai et al., 2012; Yaffe et al., 2015). In cancer cells, piperine leads to p21 and caspase activation, which causes cell cycle arrest and apoptosis, respectively (Fofaria et al., 2014). Piperine also exerts other anticancer mechanisms, including the regulation of cellular redox

TABLE 3 In vivo and in vitro cancer studies related to the curcumin-quercetin combination.

Type of study (cancer cells, animal)	Type of drug administration	Cancer	Findings	References
Cancer cells	Curcumin–quercetin	Breast cancer	Exhibits a synergistic action in suppressing the cell survival and migration of TNBC cells by inducing tumor suppressor genes	Kundur et al. (2019)
Cancer cells	Curcumin–quercetin	Gastric cancer	Combined treatment indicates stronger anticancer efficacy than each of them alone	J. Y. Zhang et al. (2015)
Cancer cells	Curcumin–quercetin	Melanoma	Exerts synergistic effect on cancer cell proliferation	Srivastava and Srivastava (2019)
Cancer cells	Curcumin–quercetin	Chronic myeloid leukemia cancer	Demonstrates multi-targeted therapy potential for cancer cells synergistically without affecting healthy cells	Altundağ et al. (2021)
Cancer cells	Curcumin–quercetin	Prostate cancer	Sensitizes androgen resistance cancer cells to antiandrogens through the reduction of epigenetic modifications participating in methylation-dependent repression of tumor suppressor genes like androgen receptor	Sharma et al. (2016)
Animal	Curcumin–quercetin	Lung carcinogenesis	Exerts benefit effects on drug metabolizing enzymes and antioxidant status	Liu, Wu, Yu, et al. (2015)
Animal	Curcumin–quercetin	Lung carcinogenesis	Increases apoptosis through modulation of p53 posttranslational modifications	P. Zhang and Zhang (2018)

TABLE 4 In vivo and in vitro cancer studies related to the curcumin-piperine combination.

Type of study (cancer cells, animal)	Type of drug administration	Cancer	Findings	References
Cancer cells	Curcumin and piperine	Breast cancer	The combination may serve to limit stem cell self-renewal through an inhibitory effect on Wnt signaling	Kakarala et al. (2010)
Cancer cells	Curcumin and piperine	Colorectal cancer	Inhibits tumorigenesis and inflammation by repressing mTORC1 signaling	Kaur et al. (2018)
Animal	Curcumin and piperine	Prostate carcinogenesis	Exerts protective effect on prostatic lesions	Facina et al. (2021)
Animal	Curcumin and piperine	Hepatocellular carcinoma	Exhibits synergistic action in the suppression of carcinogen-induced-hepatocellular carcinoma	Patial et al. (2015)

homeostasis, self-renewal suppression of cancer stem cells, modulation of endoplasmic reticulum stress, and autophagy (Rather & Bhagat, 2018). Piperine significantly inhibits several cell survival regulators, including NF-κB, c-Fos, CREB, and ATF2 (Pradeep & Kuttan, 2004). It has been reported that the antimetastatic behavior of piperine has been associated with the down-regulation of MMP-9 and MMP-3 in a 4T1 murine breast cancer model (Lai et al., 2012). Shoba et al. have reported that piperine improves the bioavailability and extent of curcumin absorption in animals and healthy humans (Shoba et al., 1998). Piperine improves curcumin efficacy on stem cell self-renewal of the breast. Moreover, curcumin plus piperine has been indicated to have a stronger inhibition influence on Wnt signaling, as a self-renewal regulator of breast, in breast cancer cells than each of them alone (Kakarala et al., 2010). Evidence demonstrates dysregulation of Wnt signaling in human breast tumors (Lindvall et al., 2007). Thus, this combinatory treatment can target the self-renewal of breast cancer cells. Stearoyl-coenzyme A desaturase-1 (SCD1), a lipid desaturation enzyme, plays a key role in the self-renewal of breast cancer stem cells. A study conducted by Colacino et al. reported that the expression of SCD1 could be down-regulated by curcumin plus piperine treatment (Colacino et al., 2016).

In another study, the synergistic effect of curcumin and piperine combination has been reported in carcinogen-induced-hepatocellular carcinoma (HCC). The combined treatment indicated better inhibitory effects on HCC in evaluating apoptosis and cell proliferation than pure curcumin (Patial et al., 2015). As another anticancer effect, curcumin and piperine combination led to more suppression of mechanistic target of rapamycin complex (mTORC1) activity versus pure curcumin, indicating additivity of their effects on colorectal adenocarcinoma (Kaur et al., 2018). mTOR complex exerts a principal function in

TABLE 5 Summary of nanoformulation curcumin with other phytochemicals in vitro.

Types of cancer	Co-delivery system	Treatment	Cancer cell lines	Findings	References
Hepatocellular carcinoma	Polymeric nanoparticles	Curcumin–resveratrol	HepG2 cells	Reduces phytochemicals dosage, enhance their bioavailability, and increase their concentration at the tumor target site	Zheng et al. (2022)
Melanoma	Solid lipid nanoparticles	Curcumin–resveratrol	SK-MEL-28 cells	Strong synergistic inhibition in melanoma cell proliferation	Palliyage et al. (2021)
Prostate cancer	Dual cancer-targeted nanoparticle composed of hyaluronic acid and fucoidan	Curcumin–epigallocatechin-3-gallate	PC3 cells	The dual-targeted system exhibited more uptake and greater anticancer effect than a combination solution of phytochemicals	Chu et al. (2019)
Colorectal adenocarcinoma	Poly(N-vinylpyrrolidone) (PVP) nanoparticles	Curcumin–Epigallocatechin-3-gallate	Caco-2 cells	Enhances cellular uptake and efficacy of encapsulated curcumin in the presence of epigallocatechin-3-gallate	Y. Chen et al. (2022)
Breast cancer	Apoferritin nanoparticles	Curcumin–quercetin	MCF7 cells	Increases bio-availability and specific targeting	Mansourizadeh et al. (2020)
Ovarian, leukemia, hepatoma, cervix, colon, and lung cancers	Polymeric nanoparticles	Curcumin–quercetin and curcumin–piperine	Ovkar-3, HL60, HEPG2, HeLa, Colo205 and A549 cell lines	Enhances synergistic effects of anticancer activity	Chidambaram et al. (2014)
Ovarian carcinoma	Solid lipid nanoparticles	Curcumin–piperine	A2780/Taxol-resistant ovarian carcinoma cells	Manages multi-drug resistance (MDR) and inhibit drug-resistance cancer cells compared with free curcumin and free curcumin–piperine	J. Tang et al. (2017)
Glioma cancer	Gold nanoparticles	Curcumin–piperine	U-251 MG glioblastoma cells	Enhances the properties of combinatorial curcumin–piperine and trigger caspase-3-related apoptosis	Javed et al. (2021)

molecular processes involved in chronic inflammation that contribute to the carcinogenesis of colon cancer, including up-regulation of pro-inflammatory cytokines, enzymes associated with inflammation, and activation of intestinal immune cells (K. Wang & Karin, 2015). In addition, pretreatment with this compound has shown a stronger inhibitory effect on DNA adducts induced by carcinogenic metabolites versus each of them alone. As a result, it can reduce the risk of causing cancer due to DNA adducts (Sehgal et al., 2013). Moreover, the anticarcinogenic effect of this combination has been reported in prostatic lobes (Facina et al., 2021). Table 4 summarizes the in vitro and in vivo studies investigating the anticancer effects of the combination of curcumin and piperine.

Nanoformulation of curcumin and piperine could improve the properties of each other, particularly in bioavailability and absorption function. It has been shown that solid lipid nanoparticles with drug efflux pump inhibitory components, TPGS and Brij 78, can exert a favorable performance in managing MDR in cancer. By encapsulating curcumin and piperine in the nanoformulation, drug-resistant A2780/Taxol cells are more inhibited than that treated with free curcumin and free curcumin–piperine (J. Tang et al., 2017). In another study, it has been shown that piperine emulsome in combination with curcumin emulsome demonstrates an additive contribution to the anticancer efficacy of curcumin on the HCT116 colorectal cell line. Anticancer efficacy of this combinatory treatment includes cell cycle arrest at the G2/M checkpoint, the over-expressed gene of caspase3, and the increase in apoptotic cell percentage (Bolat et al., 2020). In addition, the improvement of the use of phytochemicals was reported in the co-encapsulated form with gold nanoparticles to overcome the poor bio-availability along with better cross-through the blood–brain barrier in the treatment of glioma cancer. The treatment of glioma cancer cells with these hybrid nanogels caused the induction of caspase-3, which is related to the alteration of the cellular F-actin cytoskeleton (Javed et al., 2021). Therefore, the curcumin and piperine combination has shown various anticancer activities due to the promotion of their features together. However, more molecular studies need to be done on this compound.

Co-drug delivery system-based nanoparticles are an efficient approach to enhance the anticancer efficacy of the phytochemical combinations (Table 5). Collectively, the synergistic effects of curcumin with other phytochemicals on cancer are worthy of attention. In addition, nanoencapsulation of the combined phytochemicals by co-delivery systems can enhance their absorption and stability. Figure 1

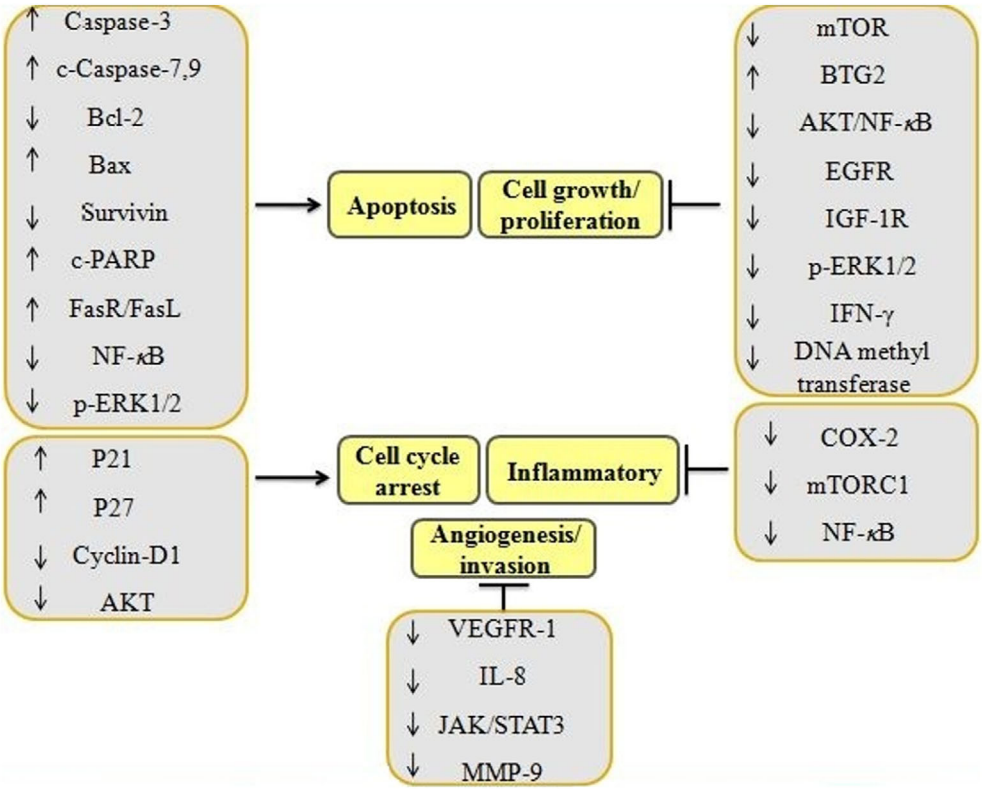

FIGURE 1 Multi-molecular anticancer target of co-treatment curcumin with other phytochemicals in cancer-related studies. Co-administration of curcumin with other phytochemicals such as resveratrol, epigallocatechin-3-gallate, quercetin, and piperine improves the synergistic effect through modulating multiple signaling pathways and inhibits cancers such as prostate, breast, head, and neck, colorectal and chronic myeloid leukemia. Akt, protein kinase B; Bax, Bcl-2 associated X protein; BTG-2, B-cell translocation gene-2; c-Caspase-7/9, cleaved-Caspase-7/9; COX-2, cyclooxygenase-2; c-PARP, cleaved-poly (ADP-ribose) polymerase; EGFR, epidermal growth factor receptor; FasR/FasL, Fas receptor/Fas ligand; IFN-γ, interferon-gamma; IGF-1R, insulin-like growth factor type 1 receptor; IL-8, interleukin-8; JAK/STAT3, Janus kinase/signal transducer and activator of transcription 3; MMP-9, matrix metalloproteinase-9; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor kappa B; p-ERK1/2, phospho-extracellular signal-regulated kinase 1/2; VEGFR1, vascular endothelial growth factor receptor 1.

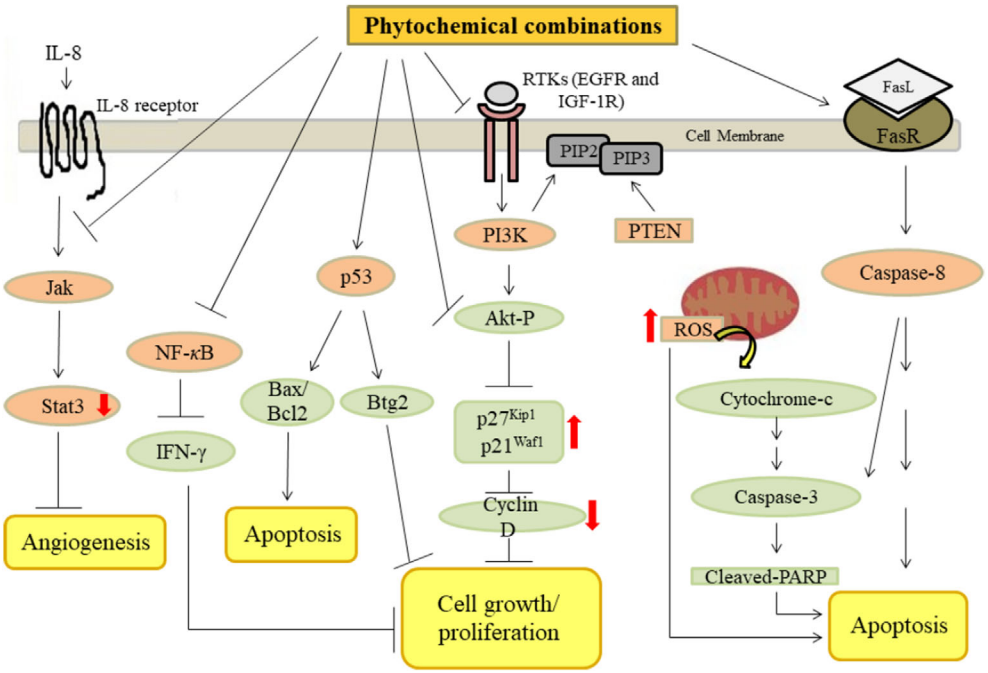

FIGURE 2 Schematic depiction of the results acquired in this study exhibiting the signaling pathways involved in the co-treatment of cancer cells with curcumin–resveratrol, curcumin–epigallocatechin-3-gallate, curcumin–quercetin, and curcumin–piperine.

summarizes the multi-molecular anticancer target of the combination of curcumin with some phytochemicals in cancer-related studies.

4 | CONCLUSION

A combined product based on plant-derived phytochemicals indicated a promising strategy to improve more effective treatment. Curcumin showed significant anticancer efficacy when combined with resveratrol, quercetin, epigallocatechin-3-gallate, and piperine. Anticancer efficacy of the phytochemical combinations may be due to their capacity to modulate various signaling pathways that inhibit cell proliferation and invasion, increase cell death, and sensitize cancerous cells. We have shown that the combinations have the potency to regulate important genes in cancer cells which were related to multiple signaling pathways regulating the cell cycle, cell proliferation, angiogenesis, and apoptosis (Figure 2). Among the studied phytochemical compounds, more studies have been conducted on the curcumin–resveratrol combination, revealing its greater molecular mechanisms and functional capabilities against various cancers. While the combination therapy of natural compounds seems to be a promising strategy, further high-quality studies are needed to firmly establish the clinical efficacy of the phytochemical combinations. It is also suggested to conduct more extensive studies along with molecular evaluation on co-encapsulation of the reviewed phytochemical combinations by nano-based co-delivery systems to improve their functionality.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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