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Editorial

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Natural products as PI3K/Akt/mTOR signaling pathway inhibitors for the management of cervical cancer

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1. Introduction

Cervical cancer (CC), a prevalent gynecological malignancy in women, presents challenges in late-stage treatment efficacy in women [1]. The PI3K/AKT/mTOR pathway is among the most frequently dysregulated pathways in patients with cervical cancer. The activation of this pathway is associated with increased cell growth and clinical outcome, and its overexpression is associated with a poor prognosis [2]. (Although there are several reviews summarizing the natural compounds targeting numerous cells signaling pathways [3] but very less or none of the review have summarized only those bioactive compounds targeting PI3K/Akt/mTOR in cervical cancer management. Therefore, this editorial aimed at summarizing only those natural compounds that inhibit PI3K/Akt/mTOR pathway as a potent therapeutic approach in cervical cancer management.

Several oncogenic signaling pathways such as (TGF-β, PI3K/Akt, JAK/STAT, MAPK/p38, Notch, NF-κB) have been identified to be associated with CC progression via modulating gene expression [4]. Thorough understanding of these cells signaling pathways and their modulating could provide new avenues for targeting cervical carcinoma. Several conventional therapeutics including radiotherapy, chemotherapy, and surgery, remains less effective and presented severe adverse reactions in cancer [5]. Hence, there is a crucial need for elucidating compounds with limiting toxicities and better therapeutic efficacy.

Bioactive compounds have been displayed as potent lead candidate for anticancer drug development via targeting numerous signaling pathways [6]. Their chemical structures facilitated them to target several signaling pathways, making them extremely useful for

anticancer drug development. Hence, the aim of this editorial is to elucidate only those natural compounds for inducing apoptosis in cervical cancer cells that is associated with the progression of cervical carcinoma via targeting PI3K/Akt/mTOR signaling pathway.

Chrysotoxine

Chrysotoxine modulate ferroptosis and the PI3K/AKT/mTOR signaling pathway for inducing apoptosis in cervical cancer cells. It is a bioactive bibenzyl compound derived from the Genus Dendrobium presenting strong medicinal application [7]. Widespread research has been utilised the anti-tumour efficacy in Chinese medicinal prescription [8]. Dendrobium comprises of varied range of chemical components (bibenzyls, erianin, and gigantol) which have displayed significant inhibitory sfficacies on CC, thereby suggesting its potential therapeutic value [9]. Zhou et al., 2025 investigated the anticancer potential of chrysotoxine in CC treatment. Their findings displayed a strong scientific foundation for the management of cervical cancer via regulating ferroptosis and the PI3K/AKT/mTOR pathway by chrysotoxine [9].

Steroidal saponin

The steroidal saponin RCE-4 isolated from *Reineckia carnea*, possess significant anti-CC potential via apoptotic induction. None of the study has investigated the antiproliferative potential efficacy autophagy induction of RCE-4. Hence, Xiang et al., investigated the detailed mechanisms associated with autophagy induction in CC cells. RCE-4-induced PI3K and ERK pathways inhibition resulted in significant anti-cancerous potential and reduced chemoresistance, compared with the PI3K and ERK, and AMPK inhibition associated with regulation of autophagy [10].

Benzimidazole derivatives

Several studies have displayed the medicinal efficacy of benzimidazole and its derivatives as potent anticancer agent, either via targeting specific molecules or cell signaling pathways [11]. PI3K/Akt/mTOR remains the most potent therapeutic target for CC treatment. Benzimidazole derivatives (anti-CC agents) work through inhibition of tubulin and PI3K/Akt/mTOR pathway. 4r induced apoptosis via PI3K/Akt/mTOR inhibition in association with cell cycle arrest in G2/M phase [12].

Cyanidin-3-O-glucoside

Cyanidin-3-O-glucoside (C3G) is a strong natural anthocyanin found in dietary flavonoid found in berries, exhibiting female reproductive health via inducing oxidative stress and apoptosis in both ovarian and CC cells. C3G can modulate estrogen receptors, growth factors, and apoptosis- and angiogenesis-related pathways [13]. Li et al., 2021 indicated C3G induced increased antitumor potential and antitumor potential of cisplatin (DDP), thereby signifying it as potential strategy to decrease chemotherapy induced adverse effects in cervical cancer. Furthermore, after C3G treatment, reduced levels of cyclin D1 and Bcl-2 and increased Bax, caspase-3, p53, and modulated PI3K/AKT/mTOR signaling pathway. Their study made a

significant revelation, for the first time, that C3G induced enhanced anticancer potential of cisplation, signifying a potent strategy to decrease the adverse effects of chemotherapy in CC [14].

6-Shogaol

6-shogaol from ginger possess various selectivity for normal and cancerous cells during treatment, that makes it more valuable for further clinical research and development. Therefore, focussing its anticancer potential, underlying mechanism and modulation of associated signaling pathways [15]. 6-Shogaol (from ginger) showed anti-tumor effect in CC via suppressing PI3K/Akt/mTOR pathway, cell arrest and metastasis and promoting cell cycle arrest (G2/M phase) in both (HeLa and SiHa) CC cells. It further induced apoptosis via mitochondrial pathway leading to downregulated p-PI3K, p-Akt and p-mTOR expression levels. It has also been found as functional food ingredient, which made it used as therapeutic agents for CC patients [16].

RCE-4 from *Reineckia carnea*

The steroidal saponin RCE-4 isolated from *Reineckia carnea*, displayed potential anti-CC activity via apoptotic induction. Wei et al., 2019 reported the RCE-4 induced autophagy. Additionally, autophagy inhibition enhanced the therapeutic efficacy of RCE-4 which highlighted it as potent candidate for CC treatment [17].
Anti-proliferative potential of RCE-4 on HeLa cancer cells via NF-κB activation and suppressed PI3K/Akt/mTOR signaling pathway. Anti-CC potential of RCE-4 by modulating PI3K/Akt/mTOR signaling pathway, NF-κB activation, and inflammation-related key factors in both cervical cancer cells. RCE-4 treatment significantly enhanced release of cellular LDH, DNA fragmentation, Bax, cleaved PARP protein levels and apoptosis alongwith reduced expression levels of PI3K/Akt/mTOR and NF-κBp65 phosphorylation, Bcl-2 protein levels in HeLa cells. These research findings suggested apoptosis induction in CC (HeLa) cells via inhibiting phosphorylation of PI3K/Akt/mTOR and NF-κB activation [18].

Magnolol

Magnolol is an organic compound that is classified as lignan. It is a bioactive compound found in the bark of the Houpu magnolia (Magnolia officinalis) and in M. grandiflora. 5-FU along with magnolol displayed synergistic anti-CC efficacy via PI3K/AKT/mTOR and epithelial-mesenchymal transition (EMT) modulation [19]. Additionally, magnolol either in combination or alone with 5-FU inhibited inhibitory potential of cell adhesion, migration PI3K phosphorylation and mTOR levels in 5-5U cells [20].

Kaempferol

Kaempferol (natural flavonoid) found abundantly in fruits and vegetables. It has various bioactivities, with antioxidant, anti-inflammatory, and other beneficial properties [21]. Kaempferol induced apoptosis and autophagy via inhibiting the PI3K/AKT/mTOR pathway in human cervical cancer cells thereby presenting it as a potential anticancer agent [22]

Piperlongumine (PL)

Piperlongumine (PL), an amide alkaloid mainly reported in long pepper, possess neuroprotective and anti-cancer potential [23]. PL treatment promoted apoptotic induction via downregulating PI3K/Akt/mTOR pathway target of rapamycin pathway in KB CC cells [24].

Formononetin (FN) and sulforaphane (SFN)

Plant-based substances along with their derivatives play significant role in the management of numerous cancerous cells by modulating the tumor microenvironment and possess cell signaling pathways [25]. Jiang et al., 2024 investigated the combinatorial effect of formononetin (FN) and sulforaphane (SFN) inhibited CC cells via impeding the PI3K/Akt/mTOR signaling pathway in HeLa cells and thereby promoted as a chemotherapeutic medication [26].

Conclusion

This editorial draw attention to the work published by several researchers on the management of cancer management by utilizing plant derived bioactive compounds via targeting PI3K/Akt/mTOR signaling pathway. Attention is paid to elucidating all possible natural lead candidate that targets PI3K/Akt/mTOR signaling pathway for the development of anticancer agent against cervical cancer. Future research should prioritize comprehensive mechanistic studies, optimization of pharmacokinetic properties, and well-designed preclinical and clinical experimentation to facilitate the successful translation of these natural products into therapeutic anticancer agents.

Author Contributions

Conceptualization, Writing, Review and Editing: Pratibha Pandey

Data Availability

No new data were created or analyzed in this study.

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None

Conflicts of Interest

None.

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