Targeting Cancer through PI3K/AKT/mTOR Pathway with Selected Natural Products (β-Elemene, Puerarin and Gypenosides)

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Abstract

The second foremost cause of mortality around the world is cancer; therefore correct therapy for its treatment is important. A number of therapies are in practice for the treatment of cancer, but the highly effective and less toxic treatments for cancer are natural products (NPs). These NPs cure the cancer through regulation of different pathways; such are PI3K/AKT/mTOR, NF-kB, autophagy, MEK-ERK, inflammation, oxidative stress and apoptosis. A group of natural product is sesquiterpene lactone (SLs) among which β-elemene (ELE) and Puerarin (Pue) are well known due to its anticancer activities. Other NPs, Gypenosides (Gyp) also possessed potent anticancer effect. Although these NPs have possess potential effect against cancer, but its anti-cancer mechanism through PI3K/AKT/mTOR pathway are need to be summarized. Therefore, we summarize it and hope this review will provide a baseline for further research on these compounds via PI3K/AKT/mTOR pathway.

Keywords: Sesquiterpenelactone , β-elemene, Puerarin, Gypenosides

Introduction

The second foremost cause of mortality around the world is cancer; therefore correct therapy for its treatment is important [1,2]. The highly effective and less toxic treatment for cancer are natural products (NPs) [1] its vital source is medicinal plants [3,4]. These NPs cure the cancer through regulation of different pathways, such are PI3K/AKT/mTOR, NF-kB, autophagy, MEK-ERK, inflammation, oxidative stress and apoptosis [3]. A group of NPs are sesquiterpene lactones (SLs) and belong to the C15 terpenoids group. SLs possess different biological and pharmacological activities including anti-inflammatory and anti-cancer [4].

Among SLs, ELE is well known due to its anti-cancer effect against a variety of cancers [5]. ELE is derived from Rhizoma Zedoaire, which is a dry rhizome consist of Curcuma phaeocaulis, Curcuma khangiensis and Curcuma wenyujin. (1) It is approved by the Chinese ministry of health for cancer treatment [1]. In a variety of cancers, ELE induces apoptosis through different mechanism including PI3K/AKT/mTOR pathway.

Another important and approved NP from the Chinese Ministry of Health is Puerarin for the treatment of different diseases [3]. Pue is derived from a number of plants, such as Pueraria lobata.
(Wild) ohwi, Pueraria tuberosa (Wild) and Pueraria thomsonii Benthi [3]. Pue cure cancer through different mechanisms but here we will summarize its activities against cancer through PI3K/AKT/mTOR pathway. Glycosides (Gyp) are another group of triterpenesaponins, derived from Gynostemmaphyllum (GpM), possess anticancer activities in vitro and in vivo. A number of clinical trials have also reported that the Gyp possess the potential effect against cancer [6]. The Gyp is popular folk medicine in China and used for the treatment of different diseases including, hepatitis [7], hyper-lipoproteinemia [8] and cardiovascular diseases [9]. Furthermore, in a number of cancer cell lines including, oral cancer SAS cells [10] SW620, [2,11] and cervical epidermoid carcinoma cells have been reported [12]. Gyp inhibits the migration, invasion, metastasis, proliferation and induces apoptosis in a variety of cancers, including lung, hepatocellular, oral, colorectal and leukemic cancer through different mechanisms including PI3K/AKT/mTOR pathway [2].

**PI3K/AKT/mTOR Pathway and Cancer**

Phosphotidylinositol-3-Kinase, Protein Kinase B and mammalian Target-of-Rapamycin signaling pathway increases the cell growth and survival by different mechanisms [13,14]. A plethora of research has reported that, this pathway overexpressed in a variety of cancers [15-18]. For example, the AKT is activated, when its two residues including serine 473 (Sr 473) and threonine (Thr 308) become phosphorylated [19]. After activation, AKT enter into the nucleus, where they change the functions of transcription regulating factors. PI3K/AKT signaling increases the mTOR expression which leads to a poor prognosis. NPs reportedly inhibit the PI3K/AKT/mTOR pathway in cancer cells [20]. The highly effective and less toxic treatment for cancer are natural products (NPs), [1] its vital source is medicinal plants [3,4]. These NPs cure the cancer through regulation of different pathways, including PI3K/AKT/mTOR [3].

**Targeting cancer through Autophagy with ELE, PUE and Gyp**

Phosphotidylinositol-3-Kinase, Protein Kinase B and mammalian Target-of-Rapamycin signaling pathway increases the cell growth and survival by different mechanisms [13,14]. Among NPs, ELE induces apoptosis in cancer cells through different mechanisms including PI3K/AKT/mTOR pathway. In different cancer cell lines including, FTC-133, human breast cancer cells (MDA-MB-468 and MCF-7) and human gastric cancer cells (SGC7901 and MGC803) ELE regulate the PI3K/AKT/mTOR pathway [21-24]. ELE regulate this pathway through inhibition of PI3K, which further inhibit AKT, mTOR and p70S6K1 respectively and lead the cells to apoptosis [21-24]. The effect of ELE on PI3K/AKT/mTOR pathway is further summarized in Figure 1. Another, well know natural product is Pue [3] which induces apoptosis in different cancer cell lines including human-mental lymphoma Z138, [25] bladder cancer T24 and EJ cells through PI3K/AKT/mTOR pathway. [25,26] In this pathway, Pue down-regulate PI3K [25], Akt [26], p-mTOR [26], and p-p70S6K [25,26]. This pathway is further summarized in Figure 1.
Gyp is also a potential NP, inhibit the proliferation in a number of cell lines. Gyp inhibits the SCC-4, SAS and PDGF-induced rat hepatic cell proliferation through regulation of PI3/AKT/mTOR pathway via inhibition PI3K, AKT, and p70S6K phosphorylation [10,27,28]. Next in SCC-4 and SAS cells, Gyp target PI3/AKT/mTOR pathway through inhibition of son of seveless (SOS), RAS, uPA and FAK, which further inhibit PI3K and Rho-A. As a result, they inhibit MMP-2,7,9 and ultimately inhibit cell migration, metastasis and invasion as shown in Figure 1 [10,28].

Conclusion

NPs play important role in cancer therapy through different mechanisms, including PI3/AKT/mTOR pathway. Among NPs, ELE, Pue and Gyp target cancer through PI3K/AKT/mTOR pathway. These NPs target PI3K/AKT/mTOR pathway through inhibition of PI3K, which further inhibit AKT, mTOR and p70S6K1 respectively and lead the cells to apoptosis. Furthermore, Gyp target PI3/AKT/mTOR pathway through inhibition of son of seveless (SOS), RAS, uPA and FAK, which further inhibit PI3K and Rho-A. As a result, they inhibit MMP-2,7,9 and ultimately inhibit cell migration, metastasis and invasion as shown in Figure 1.

Conflict of Interest

The authors declare no conflict of interest.

Consent for Publication

All authors agree to be published.

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