



Mini review

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Targeting Cancer Through NF-KB Pathway with Selected Natural Products (β -Elemene, Puerarin and Gypenosides)

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Abstract

Cancer is the second leading cause of mortality around the world; therefore, its immediate treatment is very necessary. Natural products (NPs) are considered more effective and less toxic among all therapies. The vital sources of these natural products are medicinal plants. Various studies have reported that the NPs cure cancer through modulation of the NF-kB pathway. Among the NPs, β -Elemene (ELE), Puerarin (Pue) and Gypenosides (Pue) possess potent anti-tumor effect via regulation of NF-kB pathway; therefore we summarize the available studies to provide a baseline for further research on these NPs.

Keywords: Cancer, Natural products, β -Elemene, Puerarin, Gypenosides

Introduction

Cancer is the second leading cause of mortality around the world, therefore, its immediate treatment is very necessary [1-4]. Natural products (NPs) are considered more effective and less toxic among all therapies [1,3, 4]. The vital source of these natural products is medicinal plants [5,6]. NPs cure cancer via modulation of different molecular pathways, including NF-kB, MEK-ERK, autophagy, PI3K/AKT/mTOR, oxidative stress, inflammation and apoptosis [5]. Sesquiterpene lactones (SLs) are a group of NPs belong to C15 terpenoids group. These SLs possesses a variety of pharmacological and biological activities including anti-cancer and anti-inflammatory [6].

In SLs, ELE possess potent anticancer effect against different cancers [7]. The source of ELE is Rhizoma Zedoaire, which I dry rhizome of *Curcuma khangsiensis*, *Curcuma wenyujin* and *Curcuma phaeocaulis* [1]. The Chinese ministry of health has been approved ELE for the treatment of cancer [1]. ELE induces apoptosis through different mechanisms, including NF-kB pathway. Next, Puerarin (Pue) is also an NP derive from *Pueraria lobata* (Wild) ohwi, *Pueraria tuberosa* (Wild) and *Pueraria thomsonii* Benth [5] and approved by the Chinese ministry of health for the treatment of different diseases [5].



The NPs Gypenosides (Gyp) belong to a triterpine saponins group which are derived from *Gynostema pentaphyllum* (GpM), having an anticancer effect both in vivo and in vitro as well used in different clinical trials [8]. Gyp has been used for the treatment of a number of diseases in China, including hyper-lipoproteinemia [9], cardiovascular diseases [10], and hepatitis [11]. Furthermore, in a number of cancer cell lines including, oral cancer SAS cells, [12] SW620, 2, [13] and cervical epidermoid carcinoma cells have been reported [14]. 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 NF- κ B pathway [2].

NF- κ B pathway and Cancer

NF- κ B (Nuclear Factor κ B) is a transcription factor complex having homo and heterodimers of five members of a Reticuloendotheliosis oncogene cellular-homolog (Rel) family, including RelB, RelA (p65), c-Rel, NF- κ B2 (p52/p100) and NF- κ B1 (p50/p105) [15]. The functions of NF- κ B is dysregulated in tumorigenesis [16]. In different cancers, including prostate, breast, pancreas, liver, colon, lymphoma, leukemia and ovarian cancers the NF- κ B has been reported inactive state [17-19]. The DNA damage in lead to activation of NF- κ B due to which NF- κ B targeted genes are becomes activated, such are cyclooxygenase-2 (COX-2) [20]

and iNOS (inducible nitric oxide synthase) [21]. Next, the TNF α binding to TNFR causes homotrimerization of the adopter and receptor proteins, causes cell survival and proliferation through enhancing the expression of NF- κ B and activator protein 1 target genes, including vascular cell adhesion molecule 1 (VCAM 1) [22-24]. Furthermore, the active NF- κ B cause the activation of chemokines and its related receptors such are C-X-C chemokine receptor-4 (CXCR-4) and CCR-7 [25] which are involved in target organs [22]. These genes are involved in the anti-apoptosis and pro-survival. It is very obvious that the NF- κ B is a candidate for therapeutic resistance in a variety of cancers. NPs possess potent therapeutic activity against different cancers through regulation of NF- κ B pathway [6, 26].

Targeting Cancer through NF- κ B pathway with NPs (β -Elemene, Puerarin and Gypenosides). One of the most important and potent NP ELE shows its anticancer activities against different type cancer cells, including RPMI-8226, SGC7901/ADM and HL-60 through modulation of NF- κ B pathways. In NF- κ B pathway, ELE inhibit NF- κ B p65, COX-2, PGE2 and lead to inhibition of cell proliferation [27-29] as depicted in Figure 1. Another NP Pue has a potent effect against different cancer cell lines including, lipopolysaccharide induced THP1 [30], Z138 [31], T24 [32], MCF-7 [33], MCF-7/ Adriamycin (MCF-7/adr) [34], and MDA-MB-231 [33].

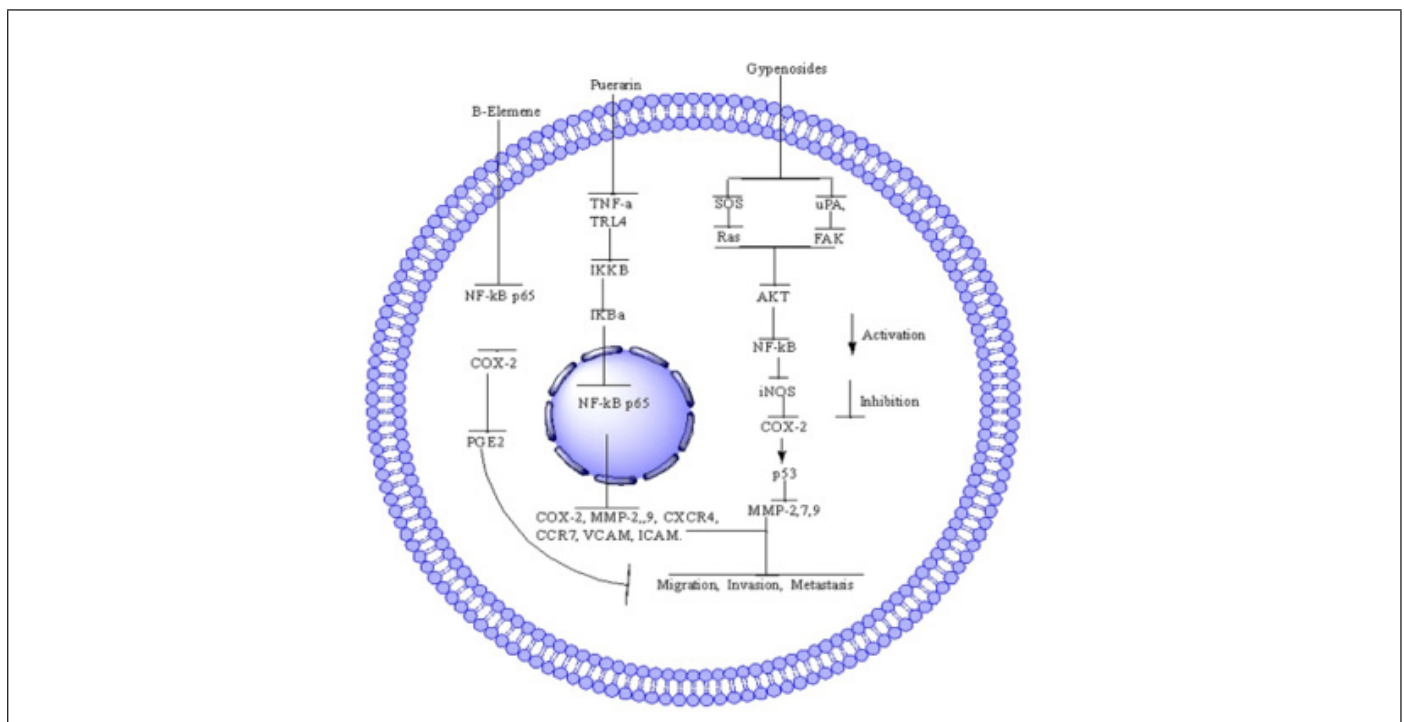


Figure 1: NPs (ELE, Pue and Gyp) and NF- κ B pathway in different cancers. In NF- κ B pathway, ELE inhibit NF- κ B p65, COX-2, PGE2 and lead to inhibition of cell proliferation. Pue downregulate the expression of TNF- α and IL-6 and Pue inhibits the expression of inflammatory factors TNF- α and IL-6 and reduce the activation of NF- κ B through downregulation of p-IkBa/IkBa, IkkappaB and p65 while increasing the expression of miR16. Next, Pue inhibit the nuclear translocation of NF- κ B [33] which result in downregulation of COX-2, MMP-2,9, CXCR-4, CCR-7, VCAM, and ICAM, both at mRNA and protein level. Gyp downregulate the SOS, RAS, uPA and FAK, which further reduces the expression of AKT, NF- κ B, iNOS and COX-2 while activating p53. Furthermore, they inhibit MMP-2,7,9 which result in inhibition of cell migration, invasion and metastasis.

In these cells, Pue negates adhesion [33], inhibit migration [33], invasion [33] and proliferation [31] through modulation of NF-kB pathway [30,31,33-35]. Furthermore, Pue downregulate the expression of TNF- α and IL-6 and Pue inhibits the expression of inflammatory factors TNF- α and IL-6 [33] and reduce the activation of NF-kB through downregulation of p-IkBa/IkBa [30, 33,34] IkkappaB [33,34] and p65 while increasing the expression of miR16 [32]. Next, Pue inhibit the nuclear translocation of NF-kB [35] which result in downregulation of COX-2, MMP-2,9, CXCR-4, CCR-7, VCAM, and ICAM, both at mRNA and protein level [33]. Natural Gyp possesses anticancer effect against SAS and SCC-4 cells through NF-kB pathway via downregulation of SOS, RAS, uPA and FAK, which further reduces the expression of AKT, NF-kB, iNOS and COX-2 while activating p53. Furthermore, they inhibit MMP-2,7,9 which result in inhibition of cell migration, invasion and metastasis [12,36] as shown in Figure 1.

Conclusions

NPs play pivotal role in cancer therapy. Among these NPs, the ELE, Pue and Gyp possesses the anti-tumor effect through modulation of NF-kB pathways. Further, the mechanisms have been summarized 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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