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Review

Natural β-Elemene : Advances in Targeting Cancer Through Different Molecular Pathways

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Abstract: Cancer is the leading cause of death around the world and its correct therapy is the need of time. Natural Products (NP)play a pivotal role in the cancer treatment and due to its high success and low toxicity, they catch the interest of scientists from the whole world. An approved NP, β-elemene (ELE) is derived from *Rhizomazedoariae* which is dryrhizome formed from *Curcuma phaeocaulis, Curcuma wenyujin* and *Curcuma kwangsiensis* . ELE potentially induces *in vitro* and *in vivo* death in a variety of cancersthrough different mechanisms including apoptosis and autophagy. This review provides a comprehensive and updated overview on cancer signaling pathways targeted by ELE.

Key words: Natural product (NP), β-elemene (ELE), *Rhizomazedoariae, Curcuma kwangsiensis,* rhizome

Introduction

Cancer is the major health problem in both developing and developed countries and the second leading cause of death around the world, with about 14 million new cases and around 8.2 million cancer-related mortality in 2012 (Ferlay et al., 2015; Khan et al., 2015).

According to an estimation of the world health organization (WHO) 17.5 million deaths are projected to occur due to cancer around the world in 2050 (Begnini et al., 2014). Along with cancer ignition and developmental factors for a specific type of cancer, many research evidences show that many cancers are the results from dysfunction of protein translated genes, including inhibitors of apoptosis, transcriptional factors, anti-apoptotic proteins, tumor suppressors and growth factor receptors provide target for treatment of cancer (Millimouno et al., 2014). Chemotherapeutic drugs are highly toxic, expensive and activate alternative signaling pathways which causes its limited success (Rahmani et al., 2014). Furthermore, highly specific drugs that target only a specific pathway like monoclonal antibodies which kill the cancerous cells through its binding to specific extracellular domain of the tyrosine kinase receptor domainalso shows sporadic response and activate the secondary resistance (Coco et al., 2012; Holohan et al., 2013; Shin et al., 2012). Cancer cannot be inhibited through mono-target therapy because cancer develops in multisteps(Faivre et al., 2006; Shu et al., 2010). Unlike mono-target pharmaceutical drugs, plants possess multi-target molecule which controls cancer progression growth through multiple mechanisms (Rahmani et al., 2014). Plants derived NP are cost-effective, safe and alternative to the modern system of treatment, therefore it gain increasing attention (Amin et al., 2009; Millimouno et al., 2014; Weng & Yen, 2012). Plants were used in cancer treatment since long time ago and remain the most attractive source of anti-cancer drugs due to millions of plant species (Balunas & Kinghorn, 2005; Chin et al., 2006; Cragg & Newman, 2005; Millimouno et al., 2014). In anti-cancer FDA approved drugs about 60% are originated from natural source, including plants (Dall'Acqua, 2014), but only about 10% of plants have been investigated for drugs (Borris, 1996; Juarez, 2014). As we know that a small part of plant flora contribute in more than 60% anticancer drugs therefore more understanding of remaining flora is necessary. Next nature spent over three billion years to create complex and wonderful complex compound library (Ogbourne & Parsons, 2014). FDA approved Only one anti-cancer drug named ‘Sorafenib’ was made through the combinatorial chemistry from 1981 to 2006 (Newman & Cragg, 2007). Comprehensive analysis of genome shows that cancer related 70% genes are similar with Arabidopsis thaliana, which show that human and plants in some cases use same pathways and receptors (Ji et al., 2009; Jones et al., 2008). As plants and human genes have similarity, therefore it is assumed that the metabolites produced by plants for their own metabolism modulation might be useful for human cancers. The example of human and plant similarity is the multi-drug resistant protein, which transport auxin in Arabidopsis thaliana, while in human the same protein carry out from the anti-cancer drugs from the cells. Auxin

modulators in Arabidopsis are flavonoids, which overcome on multidrug resistance through modulation p-glycoprotein in a variety of cancers (Taylor & Grotewold, 2005). It is proved with solid evidences that the plant base compounds inhibit cancer progression through multiple mechanisms [1] and increase the capacity synthetic chemistry (Koch et al., 2005; Monks et al., 2011). The secondary metabolites which are derived from plants are included polyphenols, terpenes and alkaloids are possessdgood anti-cancer activity (Baikar & Malpathak, 2010; Evidente et al., 2015; Lecci et al., 2014; Onrubia et al., 2013; Stahlhut et al., 2015), for example till now the number of isolated terpenes are 55,000 (Chang et al., 2010) but its anticancer value is not known very well (Tian et al., 2013). Saponins, diterpenoids and sesquiterpene lactone are the three major classes of terpenes having well known activities against a variety of human cancers (Gach et al., 2015; Sarkar et al., 2014). Therefore more compounds are necessary to identify to overcome cancer. ELE[(1S,2S,4R)-2,4-diisopropenyl-1-methyl-1-vinylcyclohexane] is sesquterpene, possess well known anti-cancer activities against different cancers through apoptosis and protective autophagy with low toxicity to normal cells (Jiang et al., 2017).ELEis less-toxic active phytochemical derived from a variety of medicinal herbs like Rhizomazedoariae(Jiang et al., 2016), *which is*dry rhizome derived from *Curcumakwangsiensis(Tohda et al., 2006)* , *Curcumaphaeocaulis* (Lai et al., 2004), and *Curcumawenyujin* (Lim et al., 2010). *Rhizomazedoariae* have anti-inflammatory, anti-microbial, antitumor and anti-proliferative activity (Maheshwari et al., 2006; Makabe et al., 2006; Park et al., 2005; Tohda et al., 2006; Zhang et al., 2014). *Rhizomazedoariae* have an active compound named ELEis approved medicine for the treatment of a variety of cancers, including lung cancers, breast, leukemia ovarian, prostate, brain and cervical cancers (Lee et al., 2012; Li et al., 2009; Li et al., 2005; Wang et al., 2005; Zhao et al., 2007; Zheng et al., 1997; Zhou et al., 2003).ELEdoes not cause any problematic toxicity to patient and patients will tolerate it (Wang et al., 2005). Advances in research on ELEshows that the anticancer activity of ELE is through targeting different molecular pathway. In these molecular pathways iscall cycle, PI3K/Akt/mTOR and MAPK pathways were reviewd by Jiang et al(Jiang et al., 2016) but not explain about other pathways including STAT3, NF-kB, Stem cell pathways and autophagy mechanism. Therefore, in this review we summarize the old and new studies about the mention pathways to encourage the scientists for further research for more accurate clinical trials.

1. Targeting Cancer through apoptosis pathways with ELE

In apoptosis genes are coordinated to perform a series of events due to which cancerous and unnecessary cells are removed (Wu et al., 2014). It can be characterized through morphological and biochemical changes including cell shrinkage, caspase-3 activation, deoxy ribonucleic acis (DNA) fragmentation and membrane blabbing(Elmore, 2007; Ferreira et al., 2002; Ouyang et al., 2012). The biological significance of apoptosis is widespread because it plays vital role in countless pathological and physiological process in different tissues. Apoptosis maintains tissues homeostasis through selective elimination of damaged or unwanted cells from tissues. Tissue homeostasis is being regulated via balance in cells proliferation and apoptosis. The disruption of this type tissues homeostasis between cell proliferation and apoptosis elevate chronic pathological conditions, including neuro-degeneration, tumerogenesis, developmental abnormalities as well as auto-immune diseases (Fuchs & Steller, 2011; Ouyang et al., 2012; Patergnani et al., 2015; Volkmann et al., 2014). Apoptosis inhibition causes drug resistance and tumerogensis(Fulda, 2015). Tumour cells inhibit apoptosis by using different types of molecular mechanisms (Hassan et al., 2014). Therefore, it is the need of the current era to activate those molecular mechanisms through which apoptosis are regulated.In current era the focus of anti-cancer drugs discovery is to identify new therapeutic compound which have the ability to activate apoptosis and eliminate the cancer from human society. Natural products (NP) catch the interest of scientists to cure the cancer. ELEis one of the NP active apoptotic compounds against different cancers. In SGC7901/ADM stomach cancer, C6 glioma, human SHG-44 glioma cells, A549 cells, HEp-2 cells, K562 leukemia cells, NCI-H292 cells, DLD-1 cells, ELE induces apoptosis through oxidative stress via inhibition of Glutathione (GSH) and increase reactive oxygen species (ROS) generation (Wang et al., 2006),as oxidative stress generates they inhibit the NF-kB(Xie et al., 2011; Yang et al., 1996) hypoxia-inducible factor 1α (HIF-1α) and survivin(Zou et al., 2014),basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and eukaryotic initiation factor (eIFs (4E, 4G)) proteins(Tao et al., 2006), activate ERK1/2, p38 mitogen-activated protein kinase (MAPK) and inducible oxide synthese (iNOS) (Li et al., 2017; Xie et al., 2011), targeting mitochondrial dependent pathway through downregulation of Bcl-2, Bclxl and upregulation of BAX (Li et al., 2017; Xie et al., 2011; Xu et al., 2005; Yuan et al., 1999; Zou et al., 2015), as a result cytochrome c as well as apoptosis inducing factor (AIF) release from mitochondria which lead to the activation of caspase-3, PARP due to which DNA fragmentation happen in the nucleus (Hu & Xu, 2008; Wang et al., 2006; Yuan et al., 1999; Zou et al., 2014)and lead the cells to apoptic death as further summarized in Table 1, Figure 1.

2.Targeting cancer cells by ROS-mediated apoptosis with ELE

Reactive oxygen species (ROS) play a vital role in different types of cellular processes, including gene expression, cell survival, proliferation, differentiation, enzyme regulation, eliminating foreign particles and pathogens (Gorlach et al., 2015a; Gorlach et al., 2015b). Multiple studies show that in cancer cells the oxidative stress is high which increase cell proliferation, survival, metastasis, angiogenesis, disrupts cell death signaling and drug resistance (Hong et al., 2015; Trachootham et al., 2009; Zhu et al., 2015a). Although ROS promotes tumour while recent studies suggest that this property of ROS can be beneficial for cancer therapy. Various *in vitro* and *in vivo* experiment shows that the Phytochemical induce exogenous ROS generation above a threshold level in cancer cells, which selectively kill these cancer cells (Seo et al., 2015; Trachootham et al., 2009; Wei et al., 2015; Zhu et al., 2015a). Plant derived NP ELEinduces ROS generation in various types of cancers. In A549, A549/DDP, human rheumatoid arthritis fibroblast-like synoviocytes ELE increase the ROS generation (Li et al., 2011; Liang et al., 2012; Liu et al., 2017; Yao et al., 2014; Zou et al., 2016) which causes the endoplasmic reticulum stress through PERK/IRE1a/ATF6 pathway (Liu et al., 2017), disrupt mitochondrial membrane potential (MMP) and activate p38 mitogen activated protein kinases which lead the cells to apoptosis (Zou et al., 2016) as summarized in Table 1 and Figure 1.

3. Targeting cancer through JAK2/STAT3 Pathway with ELE

Signal transducer and activator of transcription 3 (STAT3) pathway is involved in different cellular processes like immune function, differentiation, proliferation, epithelial to mesenchymal transition (EMT) development and survival (Siveen et al., 2014). STAT3 activation occurs by its phosphorylation at serine 727 (S727) or tyrosine 705 (Y705) (Huang et al., 2014; Qin et al., 2008). It can also be activated via cytokine receptors, growth factor receptors, abelson murine leukemia (Abl) family kinases, sarcoma (Src) family kinases and Janus activated kinases (JAK)(Harada et al., 2014; Kim et al., 2014). They also expressed in different types of tumors (Demaria et al., 2010; Yu et al., 2007; Zhou et al., 2010). STAT3 activation leads to tumerogenesis, resistance to chemotherapy, and transformation (Zhao et al., 2011). In the light of these findings activated STAT3 targeting in cancer therapy will be a novel target which may play a role in development of anticancer drugs against STAT3. STAT3 activation takes place through many signaling pathways, therefore it is necessary to identify new small molecules which inhibit STAT3 through many pathways might be helpful

in cancer therapy. A small molecule ELEwith cisplatininhibit growth and induces apoptosis in gingival squamous cell carcinoma cellsand xengraft model through inactivation of STAT3 pathway via inhibition of JAK2 phosphorylation, which lead to inhibition of STAT3 phosphorylation(Huang & Yu, 2017). Furthermore it inhibit Nasopharyngeal carcinoma cell growth through enhances zeste homolog 2 (EZH2) and decreasing the expression DNA methyltransferase 1 (DNMT1) protein and STAT3 phosphorylation (Wu et al., 2017) as further summarized in Table 1, Figure 1.

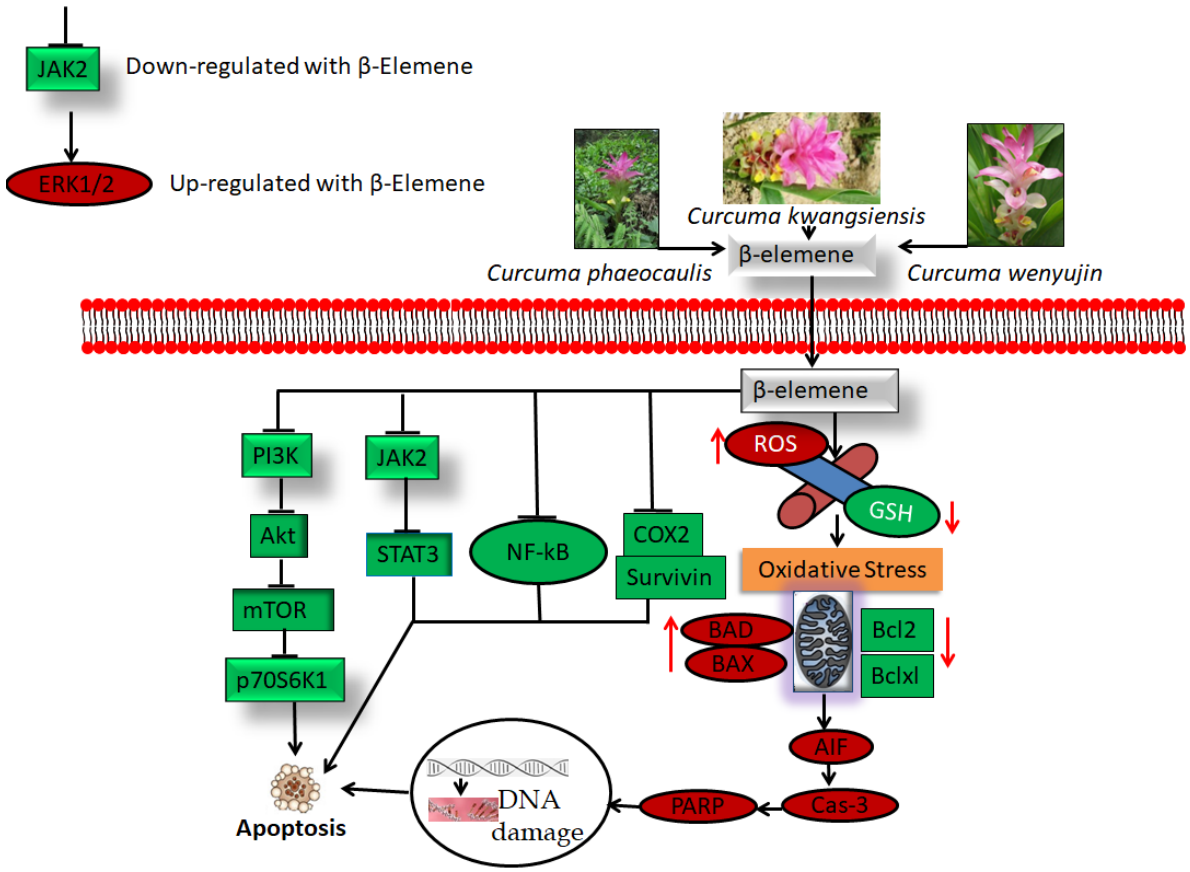

Figure 1:ROS, Mitochondrial dependent, NF-kB, STAT3, PI3K mTOR pathways. β-elemene target the cancer though different pathways. ELE increase the ROS level and decrease GSH which induces oxidative stress and mitochondrial membrane potential decrease and modulate mitochondrial protein which lead to increase in activate caspases and parp which lead to DNA damage, increase apoptosis. Further it inhibit the COX-2, Survivin and target NF-kB, STAT3, PI3K mTOR pathway and lead to apoptosis.

4. Targeting cancer through PI3K/AKT /mTOR Pathway with ELE

Phosphatidylinositol-3-Kinase/protein kinase B/ mammalian target of rapamycin (PI3K/AKT/mTOR) Pathway signaling increase cell survival and growth through different mechanisms(Courtney et al., 2010). (Steelman et al., 2011). In different types of human

cancers PI3k/AKT pathway is overexpressed through different mechanisms (Kang et al., 2006; Samuels & Velculescu, 2004; Samuels et al., 2004; Wong et al., 2010). Phosphorylation of two residues, serine 473 (Ser473) and threonine 308 (Thr 308) lead to the activation of AKT (Vincent et al., 2011), which enter into the nucleus after activation. In nucleus, they affect the activity of several factors which regulate the transcription. Phosphorylation of mammalian target of rapamycin (mTOR) occurs due to PI3k/AKT signaling and its overexpression is associated with poor recovery. NPcatch the interest of scientist to kill the cancer through different mechanisms. In the NP, ELEtarget different cancer through different mechanisms, including PI3K/AKT /mTOR Pathway.In MDA-MB-468 and MCF-7 human breast cancer cells , 549 cells, Human gastric cancer SGC7901 and MGC803 cells, FTC-133 cell lines ELE modulate the PI3K/AKT /mTOR Pathway via inhibition of PI3K, which further inhibit Akt, mTOR and p70S6K1 respectively and lead the cells toward apoptosis (Liu et al., 2012; Liu et al., 2011; Tong et al., 2013; Zou et al., 2014). Furthermore ELE also inhibit the HIF-1α gene, Survivin gene and 4EBP1(Tong et al., 2013; Zou et al., 2014) which shows that the other genes are also involved in ELE induced apoptosis. These studies reveal that due to the ELEpotent anti-tumuoraction; overcome on drug resistance and mTOR pathway inhibition shows that the ELEto be a novel anti-tumour agent which need further research. Table 1, Figure 1.

5. Targeting cancer through MAPK/ERK (Ras-Raf-MEK-ERK) Pathway with ELE

Mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is also known Ras-Raf-MEK-ERK pathway possess several cascade but mostly deregulated one is Ras-Raf-Mek-extracellular signal-regulated kinase-1 and 2 (ERK1/2) in human cancers (Santarpia et al., 2012). It regulates many functions of the cells including apoptosis, differentiation, cell growth, proliferation, senescence and migration (Chang et al., 2003). The MAPK/ERK pathway molecules are activated through its phosphorylation. When ERK is activated, they enter into the nucleus where transcriptions factors phosphorylation occurs due to it. When these transcription factors phosphorylate they bind to the promoter region of various genes including cytokines and growth factors, genes which are responsible for reduction in apoptosis and elevation in cell proliferation (McCubrey et al., 2008). When the normal signaling of this pathway becomes a failure, then they lead to senescence, drug resistance and tumorigenesis(Chang et al., 2003; Martelli et al., 2010a; Martelli et al., 2010b). In many human cancers the failure is detected in this pathway signaling (Dhillon et al., 2007; Samatar & Poulikakos, 2014). Therefore MAPK/ERK pathway targeting especially with NP

may open a new window in cancer treatment. ELEis NP inhibit the proliferation ofglioblastoma cell lines, rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS), NSCLC through MAPK/ERK (Ras-Raf-MEK-ERK) Pathway via activation of p38 mitogen activated protein kinases (p38MAPK), ERK1/2, adenosine monophosphate activated kinase (AMPK) and down-regulate the DMNT1, SP1 (Yao et al., 2008a; Zhao et al., 2015; Zou et al., 2016)and reversed through p-38 inhibitor (SB203580) pre-treatment(Zou et al., 2016), as further summarized in Table 1, Figure 2.

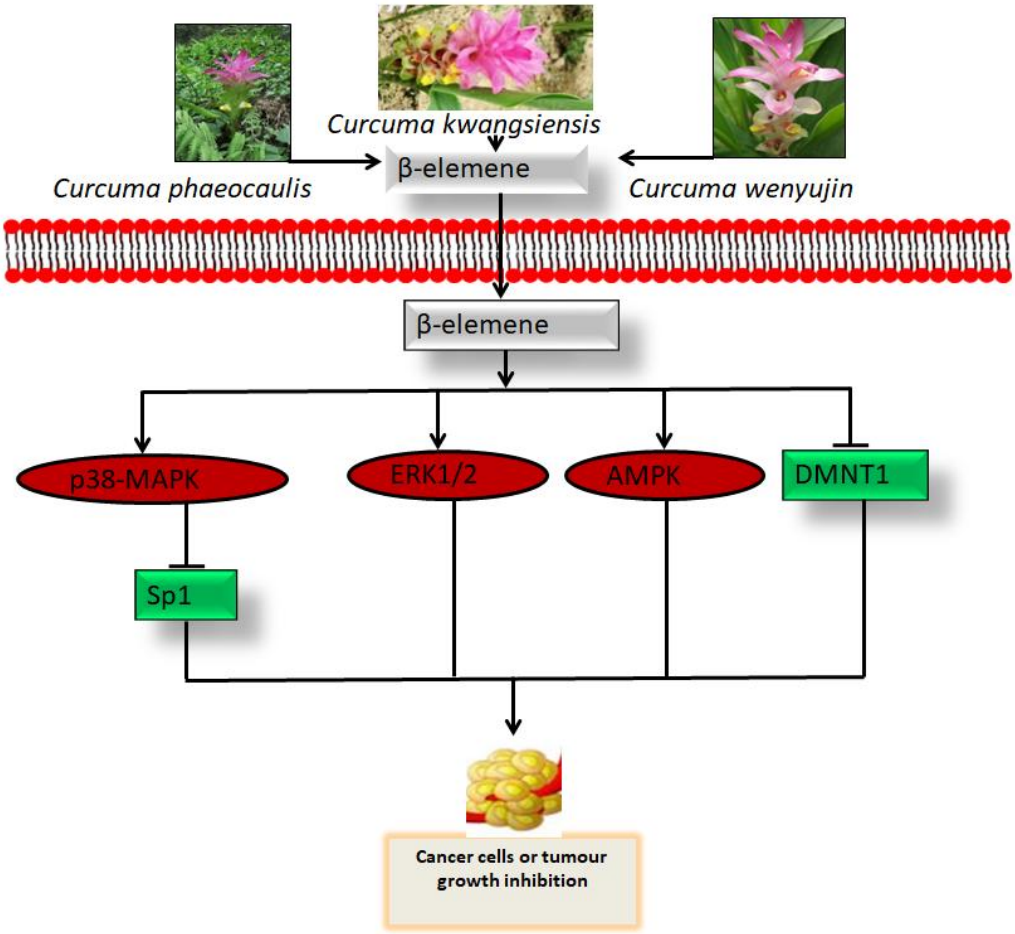

Figure 2.MAPK/ERK (Ras-Raf-MEK-ERK) Pathway.ELE target MAPK/ERK (Ras-Raf-MEK-ERK) Pathway through activation of p38-MAPK, ERK ½, AMPK and inhibit DMNT1, Sp1 and lead to tumour inhibition.

6. Targeting Cancer through Cell Cycle pathway with ELE

Cell growth is controlled by a major regulatory process called the cell cycle. It is themselves regulated at different check points by various cyclins interactions with their exact cyclin-dependent kinases (CDKs) to make active complexes. The process of each check point completes accurately before the progressionto the next phase of cell cycle (Khan et al., 2011).

Moreover, different cyclins-dependent kinases inhibitors negatively regulate CDKs. Among CDKs, p21 regulate cell cycle at different check points (Lu et al., 2006; Yang et al., 2010). Failure of checkpoints induces mutation as well as genomic rearrangements lead to genetic instability which is the cause of cancer development (Yang et al., 2010). As the new failure checkpoint due to CDKs identified, new, selective inhibiting compounds for these kinases show a potential strategy for cancer therapy. Many studies suggest that the anticancer compounds arrest the cell cycle selective checkpoints and cause death to cancer cells through apoptosis (Khan et al., 2012). Recently natural products catches the interest of scientist to discover new antitumor compounds which reverses changes in cell cycle due to check point's failure. ELE alone or in combination with etoposide or cisplatin or platinum cause cell cycle arrest in HL-60, NSCLC , glioblastoma cell lines, A549 cells, ovarian cancer, lung carcinoma H460, A549 cell lines, HepG2 cells through activation of check poin kinase 2 (ChK2)which increasecell division cycle 25C (CDC25C), p53 expression, which further activate growth arrest and DNA damage inducible protein 45 alpha (Gadd45), kinase inhibitor protein (KIP)family ($p21^{waf1}$and $p27^{kip1}$), the activation of Gadd45, p21waf1, p27(kip1) and CDC25C result in down-regulation of CDC-2, cyclin B1 and CDK-2, in the result of which FAS/ FASL activate and the cell goes to G2/M phase cell cycle dependent apoptosis (Dai et al., 2013; Lee et al., 2012; Li et al., 2013a; Li et al., 2005; Wang et al., 2005; Yang et al., 1996; Zheng et al., 1997; Zou et al., 2013). Furthermore, in glioblastoma cells, ELE induces cell cycle arrest through activation of p38MAPK, phospho mitogen activated protein kinase kinase 3,6 (pMKK3,6) which further activate the FAS/ FASL, result to G0/G1 phase cell cycle aresst due to which cell proliferation become inhibited(Li et al., 2014; Yao et al., 2008a; Yao et al., 2008b; Zhu et al., 2011) as further summarized in Table 1, Figure 3.

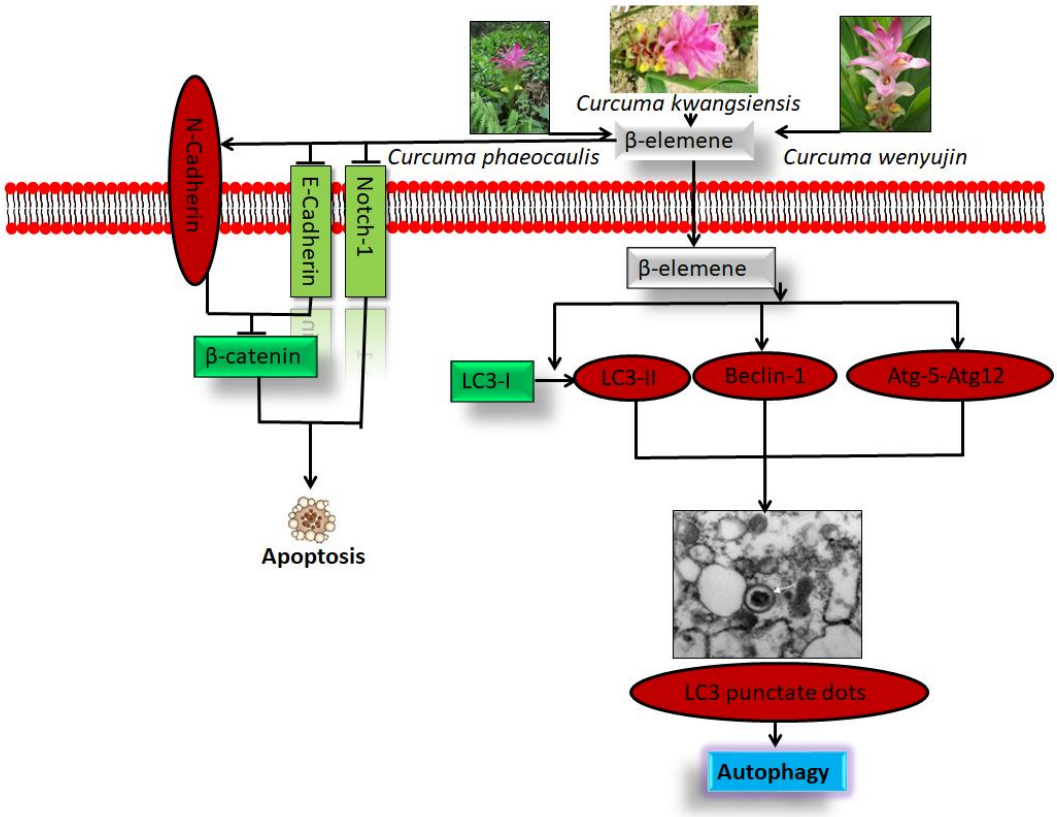

Figure 3: Cell cycle arrest.ELE causes cell cycle arrest at G2-M phase through upregulation of ChK2, p53, P27kip1, CDC25C, P21cip1, GADD45, FAS/FASL and down-regulate the CDC2, cyclin B1, CDK2, G1-phase arrest through inhibition of CD1 and RB and G1-G0 phase arrest though up-regulation of p-p38MAPK, p-MKK3,6.

7. Targeting cancer through NF-kB pathway with ELE

Nuclear factor kappa B (NF-κB)which is discovered before 30 years now becomes the central understanding of immune system (Sen & Baltimore, 1986). NF-kB is involved in different activities in the body, including activation and development of innate immune cells, negative and positive selection of thymocyte, cytokine production, Ig class switching and in haematopoiesis(Gerondakis & Siebenlist, 2010; Hayden et al., 2006). NF-kB is evolutionary conserved; regulate the inflammatory and immune responses. Several studies show that inhibitor of nuclear factor kappa-B kinase/Nuclear factor kappa B **(**IKK/NF-κB) pathway play pivotal role in the maintenance and the induction of inflammation that lead to metabolic disease like type 2 diabetes and obesity. Recent reports highlight that NF-kB regulate cellular network of aging, cancer and anticancer therapies (Tornatore et al., 2012). NF-kB family proteins are found in every type of cell and play crucial role in a variety of human cancers through regulation of cell differentiation, survival, apoptosis and proliferation which provide us clues about its deregulation during metastatic process, tumorigenesis and resistance to

tumour therapies(Li et al., 2013b).In HL-60, SGC7901/ADM and RPMI-8226 cells, ELE inhibit the NF-kB pathway thorugh inhibition of NF-kB, NF-kB p65 which further inhibit the cyclooxygenase-2 (COX-2) and as the COX-2 become inhibit they down-regulate the PGE2 and cause inhibition of cell proliferation (Chen et al., 2010; Fu et al., 2013; Zheng et al., 2009)as further summarized in Table 1, Figure 1.

8. Targeting cancer through Autophagy with ELE

Autophagy is a conserved metabolic process and past studies reported that functional and genetic link exists between cancer and autophagy, which suggest that autophagy is the mechanism of tumour suppression. In the process of autophagy cell contents are enclosed in auto-phagosomes which further attach with lysosome to degrade and thus recycle their contents (Sato et al., 2007). In cancer, autophagy is a complex process because it is not only death, but also survival process during under cellular stress(Hour et al., 2000; Yu et al., 1992). Autophagy pro-survival and death nature maybe related with cancer type, stage and sustaining of cancer cells. Although some studies show that autophagy inhibition increases apoptosis (Huang et al., 2013; Huang & Sinicrope, 2010). ELE induces autophagy inSGC7901, MGC803 gastric cancer, A549, human breast cancer, human hepatoma cancer HepG-2, SPC-A-1/DDP cells through increase in light chain 3 (LC3I)conversion to LC3II due to which Beclin1 activate, theautophagy related proteins (Atg-5-atg12) complex formed, result to LC3 punctate dot formation and lead the cells to Autophagy (Guan et al., 2014; Lin et al., 2014; Liu et al., 2012; Liu et al., 2011; Mu et al., 2016)as summarized in Table 1, Figure 4.

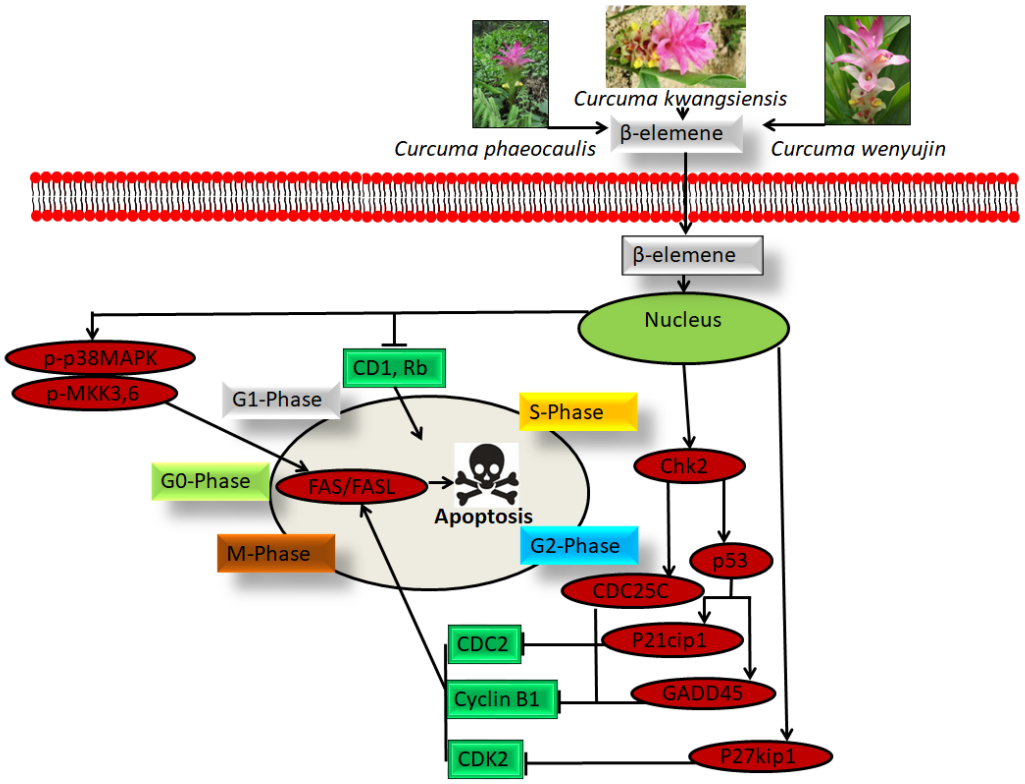

Figure 4: Stem cell pathway. ELE induces apoptosis through up-regulation of N-cadherin and down regulation of E-cadherin, β-catenin and Notch-1. ELE induces autophagy in cancer cells through conversion of LC3-I to LC3-II, up-regulation of Beclin-1, Atg5-Atg12 complex and increase in LC3 punctate dot

9. Targeting cancer through Stem cell pathways with ELE Cancer stem cells (CSCs) are less than five percent (5%) subpopulations of neoplastic cells in the tumour, which can generate new tumors in the host body. They divide asymmetrically due to which on one side, they form for tumour formation neoplastic cells while on the other side they form CSCs (Bonnet & Dick, 1997; Reya et al., 2001; Takaishi et al., 2009). CSCs are derived from differentiated cells and normal stem cells, which undergo dedifferentiation and transformation under some condition (Reya et al., 2001), which have the ability of differentiation and self-renewal (Polyak & Hahn, 2006). Additionally, it is thought that the CSCs are the cause of metastasis invasion, progression, chemo-radiotherapy resistance, tumorigenesis and makes their analysis more important (Almanaa et al., 2013; Eaves, 2008). Mutant stem cells are changed into CSCs, so the pathway which affected stem cells also could affect CSCs **(Liu et al., 2008)**, such as Hedgehog, Notch and Wnt; meanwhile some

new pathways were found in further research on CSCs.ELE inhibit proliferation and induces apoptosis in GSLCs, glioma cells through stem cells pathway via down-regulation of Notch-1, E-cadherin and up-regulation of N-cadherin due to which mesenchymal markers β-catenin inhibit and lead the cells to apoptotic death (Feng et al., 2017; Yan et al., 2013; Zhu et al., 2015b), furthermore, it down-regulate stemness markers CD133, ATP-bindingcassette subfamily G member 2,ATP-binding cassette sub-family G member 2 (ABCG2) and upregulate the glial fibrillary acidic proteinGFAP expression and sonic hedgehog(Zhu et al., 2015b; Zhu et al., 2014) as further summarized in Table 1, Figure 4.

Conclusions

ELE is a potential anticancer NPfor the treatment of different cancers including lung, breast, leukemia ovarian, prostate, brain and cervical cancers. It induces cancers cell death through different pathways including apoptosis, ROS, JAK2/STAT3, PI3K/AKT /mTOR, MAPK/ERK (Ras-Raf-MEK-ERK), Cell Cycle, NF-kB, Stem cells and autophagy. ELE target a number of cancer pathways and induces cancer cells death but still a number of pathways is undiscovered so it is needed to uncover these cancer pathways with ELE. A number of cancer approved drugs are useless due the activation of other survival pathways while ELE inhibit these pathways so it is necessary to overcome on these pathways through ELE and prevent the loss of approved drugs.

Abbreviations

Natural product (NP), β-elemene (ELE), world health organization (WHO), Fedral development authority (FDA), Reactive oxegan species (ROS), Glutathione (GSH), Hypoxia-inducible factor 1α (HIF-1α), Inducible Nitric oxide synthese (iNOS), p38 mitogen-activated protein kinase (MAPK), Nuclear factor kappa B (NF-kappa B), Apoptosis inducing factor (AIF), Signal transducer and activator of transcription 3 (STAT3), Epithelial to mesenchymal transition (EMT), Janus activated kinases (JAK), Enhances zeste homolog 2 (EZH2), DNA methyltransferase 1 (DNMT1), Serine 473 (Ser473), Threonine 308 (Thr 308), E2 transcription factor (E2F), Mammalian target of rapamycin (mTOR), Phosphatase and tensin homologue (PTEN), 13,14-bis(cyclohexamino)-belemene (IIn), Extracellular signal-regulated kinase-1 and 2 (ERK1/2), Rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS), cyclin-dependent kinases (CDKs).

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Author's contribution
All authors are equally contributed.

Conflict of interest
All authors declare that there is no conflict of interest.

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Table 1: ELE target cancer in different cell line via modulation of different genes though different mechanisms.

Mechanism	cell lines	Genes/proteins involved	Mode of action	References
Apoptosis pathways				
	Stomach cancer SGC7901/ADM	NF-kappaB	Apoptosis	[61]
	C6 glioma cells	caspase-3	Apoptosis	[69]
	SHG-44 glioma cells		Apoptosis, DNA ladder formation	[46]
	C6 glioma cells	Bcl2/Bclxl/BAX	Apoptosis	[66]
	A549 cells	p53U/DNA-PKcs/Bcl2	Apoptosis	[67]
	A549 cells	caspase-3U	ROS generation/ DNA damage/apoptosis	[77]
	A549 cells	HIF-1α/survivin	Apoptosis	[63]
	HEp-2 cells	casepase-3U/eIFs,bFGF,VEGF	Apoptosis	[149]
	HL-60 cells	Bax/Cytochrome C/Cleave caspase-3	Apoptosis	[150]
	HL-60 cells		Cell cycle arrest/apoptosis	[45]
	Hela cells	Caspase-3/Cl-PARP	DNA fragmentation/ROS generation	
	K562 leukemia cells	Bcl2	Apoptosis	[68]
	Gastric cancer cells BGC-823	BAX / p-ERK1/2U/BCL2	Apoptosis	[65]

ROS-mediated apoptosis				
	A549 cells	PERK/IRE1a/ATF6	Increase ROS level/apoptosis	[79]
	Rheumatoid arthritis fibroblast-like synoviocytes	p38/MAPK	apoptosis	[81]
	A549/DDP cells	MMP/P-gp	increase ROS level/apoptosis	[80]
	A549 cells		Increase ROS generation/apoptosis	[77]
	Osteosarcoma cells		Increase ROS /apoptosis	[78]
JAK2/STAT3 Pathway				
	Gingival squamous cell carcinoma cells	JAK2, Bcl2, p-STAT3/caspase-3 and Bax	Proliferative inhibition/apoptosis	[91]
	Nasopharyngeal carcinoma cells	STAT3/DNMT1/EZH2	Inhibit growth	[92]
PI3K/AKT /mTOR				
	Human breast cancer MDA-MB-468 and MCF-7cells	P-p70S6K1D/4EBP1D/Cl.LC3	Autophagy	[151]
	A549 cells	PI3K/Akt/mTOR/p70S6K1	Protective	[102]

			autophagy/apoptosis	
	A549 cells	HIF-1α/survivin/mTOR		[101]
	Human gastric cancer SGC7901 and MGC803 cells	LC3-II/Atg5-Atg12/ Beclin 1	Apoptosis/autophagy	[100]
	Follicular Thyroid Cancer Cells FTC-133 cell lines	In vitro AKT inhibition, *In vivo* reverse imbalance of Treg/Th17	Akt inhibition, Treg/Th17 imbalance reversing	[152]
	K562 leukemia cells	mTOR	Inhibit growth	[153]
	Human Renal-cell Carcinoma 786-0 Cells	PI3K/Akt/mTOR/ MAPK/ERK	Apoptosis, Autophagy	[154]
	A549 cell	Survivin/HIF-1α	Apoptosis	[63]
MAPK/ERK (Ras-Raf-MEK-ERK) Pathway				
	Glioblastoma cells	p38 MAPK	Cell cycle arrest /inhibit tumor growth	[110]
	Human rheumatoid arthritis fibroblast-like synoviocytes	Caspase-3/Caspase-9/ p38 MAPK	Apoptosis / reduce the cells viability	[81]
	Human lung cancer cells	Akt, ERK1/2/ AMPKa/DNMT1/Sp1	Inhibit cell growth	[111]
Cell Cycle pathway				
	Promyelocytic leukemia HL-60 cells		Cell cycle arrest/apoptosis	[45]
	NSCLC cells	P-Cdc2(Thr-161)/cyclin B1/phospho-Cdc2 (Tyr-15) p27/Cdc25C/ Chk2	Cell cycle arrest/apoptosis	[47]

	Glioblastoma cell lines	p38 MAPK	Cell cycle arrest/inhibit proliferation	[110]
	NSCLC cells A549 cells	p21, p53, Bax,Cl-PARPU/ cyclin D1	Cell cycle arrest	[155]
	Lung carcinoma H460, A549 cell lines	CHK2/ CDC2/PCDC2/CSC25C/ cyclin B1/ p27/GADD45 /p21	Cell cycle arrest	[116]
	Ovarian cancer cells	CyclinB1/ Cdc2/Gadd45/p27kip1/ p21waf1/cip1and p53/Cdc2-B1	Cell cycle arrest	[48]
	Ovarian cancer cell line A2780/CP70 parental cell line A2780		Cell-cycle arrest	[117]
	Ovarian cancer cell line A2780	Cyclin A, Cyclin B1, and CDC2,D/p21WAF1/CIP1 , p53	Cell cycle arrest	[44]
	HepG2 cells	Fas/FasL	Cell cycle arrest, Apoptosis	[118]
	Human Glioma Cells	caspase-3,8,9/ Fas/Fas/Bax/ Bcl2	Cell cycle arrest	[120]
	Human C6 glioma cells	p38 MAPKU	Cell cycle arrest	[121]
	Glioblastoma cells	p38 MAPK/p-MKK3 / p-MKK6	Cell cycle arrest	[110]
	Hela cells	Rb/ Cyclin D1	Cell cycle arrest	[156]
NF-kB pathway				
	Promyelocytic leukemia HL-60 cells	PGE2/NF-kappaB/COX2	Apoptosis	[127]
	SGC7901/ADM cells	NF-kappaB	Apoptosis	[128]

	human multiple myeloma cell RPMI-8226	BCL-2/NF-kappaB P65/DR-4/caspase-3	Apoptosis	[129]
Autophagy				
	Human gastric cancer MGC803 and SGC7901 cells	LC3-II/Atg5-Atg12 /PI3K/Akt/ mTOR/p70S6K1	Autophagy	[100]
	A549 cells	Atg5-Atg12 /LC3-II	Autophagy	[102]
	Human breast cancer cells	conversion of LC3-I into LC3-II	Autophagy/inhibit cell growth	[135]
	Human Hepatoma Cancer Cells HepG2	Cl-PARP, Cl-casepase-3,9, BAX, BCL-2, LC3I/II,	Autophagy/apoptosis	[136]
	Glioblastoma multiform cells	EGFR	Autophagy/apoptosis	[137]
Stemcells Pathways				
	Glioma Stem-Like Cells	Notch1		[145]
	Glioblastoma cells	CD133/ATP-binding cassette subfamily G member 2 /N-cadherin/ β-catenin /Notch1/ sonic hedgehog/E-cadherin		[146]
	Gastric cancer stem-like cells (GCSCs)	Notch-1	Growth suppression/attenuate angiogenesis capacity	[147]
				[148]