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Review

Tetrandrine and cancer – An overview on the molecular approach

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ABSTRACT

Tetrandrine has been known in the treatment of tuberculosis, hyperglycemia, negative ionotropic and chronotropic effects on myocardium, malaria, cancer and fever since years together. It has been known that, tetrandrine could modulate multiple signaling molecules such as kinases of cell cycle and rat sarcoma (RAS) pathway along with proteins of tumor suppressor genes, autophagy related, β-catenins, caspases, and death receptors. Moreover, tetrandrine exhibited reversal of drug resistance by modulating P-glyco protein (P-gp) expression levels in different cancers which is an added advantage of this compound compared to other chemotherapy drugs. Though, bioavailability of tetrandrine is a limiting factor, the anticancer activity was observed in animal models without changing any pharmacokinetic parameters. In the present review, role of tetrandrine as kinase inhibitor, inducer of autophagy and caspase pathways and suppressor of RAS mediated cell proliferation were discussed along with inhibition of angiogenesis. It has also been discussed that how tetrandrine potentiate anticancer effect in different types of cancers by modulating multidrug resistance under *in vitro* and *in vivo* trials including the available literature on the clinical trials.

1. Introduction

Use of chemotherapy against cancer was initiated way back in 1940s employing nitrogen mustards and antifolate drugs [1]. As of today, there are about 200 drugs approved by the FDA to treat different types of cancer, either alone or as combination of drugs [2]. Among the approved anticancer drugs, more than 75% are from natural sources (*e.g.* taxol, doxorubicine, vincristine *etc*.) and are being used either in their actual form or as simple modifications from actual form [3]. Though, majority of the chemotherapeutic drugs inhibits cancer cell proliferation by DNA damage, inhibiting the DNA replication, deregulation of enzymes/protein machineries of DNA replication and cell division as well as by inducing apoptosis, the drug action is non-specific and act on normal cell too, making the process difficult to treat cancer without any side effects/toxicity [4,5]. Hence, there is a great demand for the identification of newer and novel anticancer agents.

Natural products targeting the molecular signaling machineries of cell division and apoptosis have been considered as the foundation for the treatment of cancer for the past 30 years [6]. Microbial metabolites like mitomycin C, anthracyclinones, doxorubicin *etc.* and phytochemicals like taxol, vincristine, vinblastine, podophyllotoxin, camptothecin *etc.* are some of the leading and approved anticancer drugs from natural origin [3,6,7] where in, taxol (paclitaxel) is the most accepted drug [7–11].

Tetrandrine (Fig. 1) is a bisbenzylisoquinoline (BBI) alkaloid extracted from *Stephania tetrandra* S. Moor, a member of Menispermaceae.

Abbreviations: ADAM, a disintegrin and metalloproteinase; AKT, protein kinase B; APAF 1, apoptotic protease activating factor 1; APC, adenomatous polyposis coli; ATG, autophagy protein; BAK, Bcl 2 homologous antagonist/killer; BAX, Bcl-2 associated -X protein; Bcl-2, B-cell lymphoma – 2; Bcl-xl, B-cell lymphoma-extra large (Bcl-xL); BID, BH3 interacting domain death agonist; CD 31, cluster differentiation 31; CDK, cyclin dependant kinase; CHK, checkpoint signaling kinase; CIP/KIP, CDK interacting protein/Kinase inhibitory protein; c-MET, hepatocyte growth factor receptor; Cyc, cyclin; Cyt C, cytochrome c; DR, death receptor; EGFR, epithelial growth factor receptor; ERK, extracellular signal regulated kinase; FADD, FAS associated death domain; FAS, a death receptor ligand; FASL, FAS death receptor ligand; FDA, food and drug administration; FGF, fibroblast growth factor; FLIP, FADD-like IL-1β-converting enzyme-inhibitory protein; GEF, guanine nucleotide exchange factors; GF, growth factor; GSK 3β, glycogen synthase kinase 3 β; HAI-1, hepatocyte growth factor activator inhibitor type 1; HGF, hepatocyte growth factor; HRAS, Harvey retrovirus-associated DNA sequences; IAP, inhibitor of apoptosis protein; ICAM-1, intracellular cell adhesion molecule – 1; IFN, interferon; IL, interleukin; INK, inhibitors of CDK; KRAS, Kirsten retrovirus-associated DNA sequences; LC3, cytosolic form of light chain 3 protein; MDM 2, mouse double minute 2; MEK, mitogen activated protein kinase; MKK, mitogen activated protein kinase kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRAS, neuroblastoma retrovirus-associated DNA sequences; *p27*, *p21*, *p53*, tumor suppressor proteins; *p38*, mitogen activated protein kinase 38; PI3K, phosphatidyl inositol 3 kinase; PTEN, phosphatase and tensin homologue; RB-P, tumor suppressor retinoblastoma protein phosphorylated; ROS, reactive oxygen species; RAF, rapidly accelerated fibrosarcoma; *RAS*, rat sarcoma; RB, tumor suppressor retinoblastoma; tBID, truncated BID; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TRADD, tumor necrosis factor receptor type 1-associated death domain; TRAIL, TNF-related apoptosis-inducing ligand; VEGF, vascular endoithelial growth factor; WEE, a type of protein kinase

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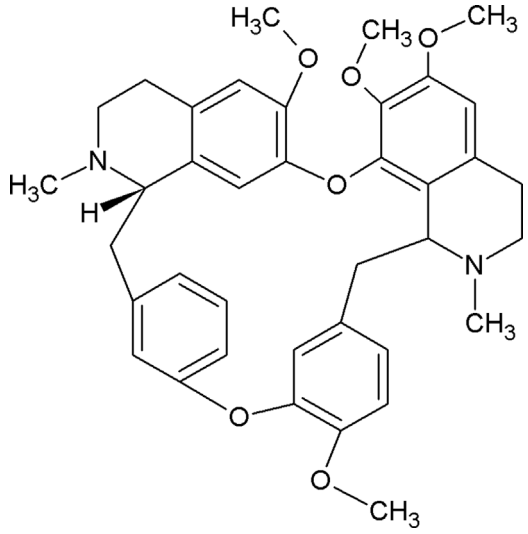

Fig. 1. Tetrandrine.

The roots of this herb is widely referred in Chinese Pharmacopoeia to treat ailments such as tuberculosis, dysentery, asthma, hyperglycemia, negative ionotropic and chronotropic effects on myocardium, malaria, cancer and fever [12–15]. Though, *Stephania tetrandra* was known for its diuretic, expectorant and cathartic activities since four hundred years [16], role of tetrandrine, as a potent calcium channel blocker [13,17,18] and as anti-inflammatory, immunosuppressant, antiallergic, antioxidant, antidiabetic, antimicrobial, anticancer and anti-Ebola agent have been reported only in 1900 onwards and are reviewed extensively by several scientists [12,19,20]. Importance of tetrandrine in cancer chemotherapy at molecular level was also reviewed recently [21] by emphasising the role of tetrandrine on cell proliferation, apoptosis, angiogenesis, metastasis, autophagy and MDR in different cancers. Indeed, the radiation sensitization property of tetrandrine, importance of nanotechnology to enhance the bioavailability, role of tetrandrine analogues and other bisbenzylisoquinoline alkaloids were also considered to review. However, the limitations involved in the use of tetrandrine as a potent chemotherapy drug have not been discussed. Therefore, in the present review, the molecular mechanism of tetrandrine targeting the cellular machineries of proliferation and apoptosis of cancer cells has been discussed and compared the mechanism of action with the other well studied anticancer drugs. In addition, suitability of tetrandrine as a chemotherapy drug and, the present challenges and future perspectives of tetrandrine as a chemotherapy drug were also discussed.

2. Signaling pathways targeted by tetrandrine

Uncontrolled proliferation of any cell due to disordered cell division accompanied by dysregulation of cell proliferation and deregulation of apoptotic signaling leads to the development of tumor [4,22,23]. Dysregulation of cell cycle occurs with the amplification of positive growth signals such as β catenin, AKT-ERK, mutations of checkpoints and surveillance genes such as CDK, cyclins, CDK-activating enzymes, CDK inhibitors, CDK substrates, and checkpoint proteins [24–26]. Also, deregulation of apoptosis occurs due to the imbalance between the production of pro and antiapoptotic proteins. Progressive cell proliferation, migration and metastasis can also associate with the aberrant activation of HGF/c-MET pathway with the loss or weak expression of plakoglobin (γ-catenin) [27,28]. Cellular migration leading to metastatic cancer might occur with the deregulation in plakoglobin mediated p-53 dependant HAI-1 expression in HGF/c-MET pathway [27]. Similar to other chemotherapy drugs under clinical use, tetrandrine also targets signaling pathways (Fig. 2; Table 1) to bring about antiproliferation and antitumor effects under *in vitro* and *in vivo* conditions. However, it is imperative to further validate the interaction and modulation of tetrandrine − protein complex to explore this compound as a promising chemotherapeutic candidate.

2.1. Cell cycle

Controlled progression of cell cycle through G_1, S, G_2 and M phases is an essential process required for the normal growth and maintenance of a healthy cell [4,22,23,29–31]. The progression of a cell through different phases of cell cycle is primarily under the control of molecular checkpoints constituting heterodimeric protein kinases with regulatory subunit (cyclin) and catalytic subunits (cyclin − dependent kinases or CDKs). Though, any change from the normal process of cell division may lead to cancer, studies revealed that multiple distinct pathways of genetic alteration such as gain of function mutations in protooncogenes and loss of function mutations in tumor suppressor genes are necessary to induce cancer [32]. Loss of function mutation in tumor suppressor retinoblastoma (RB) protein fail to bind to E_2F as mutated RB constitutively remains in phosphorylated state [33], which otherwise represses the transcription of genes necessary for DNA replication by E_2F. Likewise, mutations in INK 4 family of CDK inhibitors (CKI) like p16, p15, p18, p19 and mutated *CIP/KIP* class of protein inhibitors such as p21, p27, p53 [22,30] fail to arrest the cells at G_1 phase and DNA replication stage respectively under stress conditions. Similar to *INK* 4 and *CIP/KIP* proteins, *CHK 1* and *WEE 1* inhibitory proteins regulate the phosphorylation of CDK 1 [34,35] and, spindle attachment proteins and anaphase promoting complex (APC) control the activities of mitosis [34]. Evidences are also available on the development of several cancers including breast, liver, esophageal and multiple myelomas due to the translocation of cyclin coding genes [36–38]. Understanding the role of CDKs in cell cycle and cancer, several drugs have been developed over the past two decades to target and inhibit the function of CDKs [22,23].

Tetrandrine has been proved as check point inhibitor of cell cycle in cancer cells and prevents cell proliferation followed by apoptosis either by activation of caspase pathway or FASL mediated pathway [39–43]. Similar to 3′, 4′,7-trihydroxyisoflavone, a metabolite of soybean isoflavonedaidzein [44], tetrandrine directly inhibits CDK4, CDK2-CycE irrespective of ATP binding site of CDKs in colon, endothelial and hepatocellular carcinoma and prevents G_1-S transition of cells [41–43]. At the same time, it has also been observed that, tetrandrine does not have any role on CDK1-CycB, CDK2 – CycA and CDK6 at pharmacological concentration range. However, downregulation of hyperphosphorylated RB by tetrandrine might also contribute for the suppression of CDK4, CDK6 and CycD1 concentrations which otherwise help in G_1-S transition. In different types of cancers, tetrandrine acts as an inducer of p53 and, similar to *CIP/KIP* family proteins, the level of $p21^{CIP}$ and $p27^{KIP}$ proteins were also increased in a time dependent manner to arrest the cells at G_1 [39–41,43,45,46]. This suggests the possibility of developing tetrandrine as CDK inhibitor. Along with CDK inhibitor activity of tetrandrine, it could also enhance the proteolysis of CycD1- a key regulator of cell cycle, with an enhanced phosphorylation of Thr 286 residue in CycD1 by activated GSK 3β [47] similar to resveratrol, cycloheximide, aspirin [48,49]. Furthermore, tetrandrine induced cell cycle arrest was also observed with an inhibition in PI3K/AKT/mTOR pathway which otherwise is necessary for the cell survival, growth, migration and angiogenesis in mouse endothelial cells [50,42].

2.2. Apoptosis

Apoptosis is a process of programmed cell death required for the normal development of an organism and, also to destroy aged and infected cells [51–53]. Apoptotic cells express a variety of morphological changes including condensation of chromatin, DNA fragmentation and dissociation from the neighboring cells, shrinkage and blebbing of cell