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CURCUMIN AN ANTICANCER NATURAL PRODUCT- A REVIEW

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Abstract:
In recent years, a number of natural products isolated from Chinese herbs have been found to inhibit proliferation, induce apoptosis, suppress angiogenesis, retard metastasis and enhance chemotherapy, exhibiting anti-cancer potential both in vitro *and* in vivo. *This article summarizes recent advances in* in vitro *and* in vivo *research on the anti-cancer effects and related mechanisms of some promising natural products. These natural products are also reviewed for their therapeutic potentials, including flavonoids (curcumin)*

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INTRODUCTION:

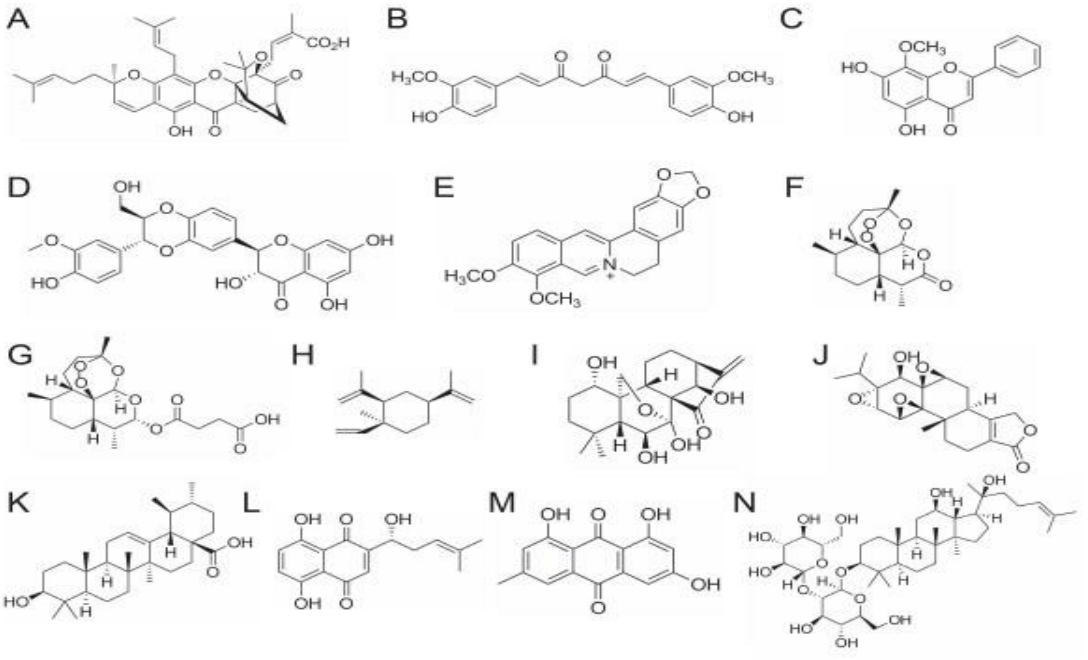
Alkaloids are important chemical compounds that serve as a rich reservoir for drug discovery. Several alkaloids isolated from natural herbs exhibit antiproliferation and antimetastasis effects on various types of cancers both in vitro and in vivo. Alkaloids, such as camptothecin and vinblastine, have already been successfully developed into anticancer drug

Curcumin

Curcumin (Figure1) is the main active flavonoid derived from the rhizome of *Curcuma longa* (*Jianghuang*), with its dry herb weight consisting of up to 3.08% curcumin [1]. Curcumin has been used to treat cardiovascular disease, inflammation and arthritis [20]. Epidemiological studies have found that incidence of several cancers is low in India where curcumin is widely consumed, suggesting that curcumin intake plays a role in cancer prevention [2]. Other studies have also indicated that curcumin inhibits cell proliferation and survival in breast cancer, colon cancer, prostate cancer, gastric cancer, leukemia, lymphoma and melanoma [3]. Curcumin induces cell apoptosis through complex intrinsic and extrinsic pathways. Curcumin binds to more than different protein targets, including transcript factors (NF-κB and activator protein-1), growth factor receptors [epidermal growth factor receptor (EGFR), human epidermal growth factor receptor , kinases [mitogen-activated protein kinase (MAPK), PKC and protein kinase A (PKA)], inflammatory cytokines [tumor necrosis factor (TNF) and interleukins], cell cycle-related proteins , matrix metalloproteinases (MMPs) and urokinase plasminogen activators (u-PA) [4,5,6]. Daily oral administration of curcumin suppresses metastasis in breast, colon, lung and medulloblastoma cancers. The suppression involves the regulation of metastatic proteins, such as vascular endothelial growth factor (VEGF), MMP-2, MMP-9 and intercellular adhesion molecules [7].

Curcumin induces non-apoptotic cell death, such as autophagic cell death, which involves the degradation of the cell's own components through lysosomal machinery [8]. *In vitro* and *in vivo* studies have demonstrated that curcumin induces autophagic cell death, as evidenced by the immunoreactivity of microtubule-associated protein light chain 3 (LC3) in myeloid leukemia cells. The action mechanism is attributed to the inhibition of the Akt/mammalian target of rapamycin/p70 ribosomal protein S6 kinase pathway and activation of extracellular signal-regulated kinase 1/2 by curcumin in malignant glioma cells [9]. In addition, autophagic inhibitor bafilomycin A1 suppresses curcumin-induced cell death [10]. Another type of non-apoptotic cell death induced by curcumin is paraptosis which is observed in malignant breast cancer cells but not in normal breast cells. Curcumin induces paraptotic events (*eg* the promotion of vacuolation accompanied with mitochondrial and/or endoplasmic reticular swelling and fusion) and decreases the level of paraptotic inhibitor protein AIP-1/Alix [11]. These paraptotic events are attributed to superoxide anion and proteasomal dysfunction [12].

Curcumin reduces toxicity induced by anti-cancer agents [13], sensitizes chemo-resistant cancer cells and demonstrates synergic effects with different chemotherapeutic agents such as doxorubicin, 5-FU, paclitaxel, vincristine, melphalan, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, suberoylanilide hydroxamic acid, dasatinib and bortezomib [14]. Prior administration of curcumin reduces the DNA damage and oxidative stress induced by cyclophosphamide (CXC) [15], improves uroprotective efficacy in the CXC hemorrhagic cystitis model [16] and suppresses early lung damage in CXC-treated rats [17]. Curcumin alleviates the side effects of mitomycin C, as evidenced by decreased lipid peroxidation and DNA damage [18]. Furthermore, curcumin reduces weight loss and improves kidney function and bone marrow suppression in animal studies [19]. When combined with oxaliplatin, curcumin decreases the proliferative capacity of oxaliplatin-resistant cell lines and enhances the cytotoxicity of oxaliplatin in an *in vitro* oxaliplatin-resistant model [20]. Additionally, curcumin protects healthy cells against radiation and sensitizes tumor cells to radiation therapy [21-24]



CONCLUSION:

Clinical trials have been or are currently being conducted to evaluate the tolerance, safety, pharmacokinetics and efficiency of curcumin as well as its combination therapy with current anti-cancer drugs. A phase I clinical trial found no dose-limiting toxicity in patients treated with an oral-dose of up to 8g/day of curcumin. The recommendation is seven consecutive doses (6g/day) of curcumin every three weeks in combination with a standard dose of docetaxel . Improvements in biological and clinical responses were observed in most treated patients [40]. A phase II trial of gemcitabine-resistant pancreatic cancer found chemotherapeutic drugs in combined use with curcumin to be sufficiently safe, feasible and efficient. While the bioavailability of curcumin is relatively poor, two out of 21 patients in the phase II trial showed clinical biological responses; one patient exhibited marked tumor regression coupled with a significant increase in serum cytokine levels .

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