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Review Article

Crude drugs as anticancer agents

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Abstract: Although tremendous progress has been made in basic cancer biology and in the development of novel cancer treatments, cancer remains a leading cause of death in the world. The etiopathogenesis of cancer is complex. Besides genetic predisposition, known environmental factors associated with cancer are: diet, lifestyle, and environmental toxins. Toxicity of drugs and eventual relapse of cancers contribute to high cancer death rates. Current therapeutic interventions for cancer- surgery, chemotherapy, radiotherapy, thermotherapy, etc. are far from being curative for many forms of cancer. Chemotherapy, in particular, though the most commonly used cancer treatment, is usually associated with side effects with varying degrees of severity. The purpose of this brief review is to assemble current literature on some crude drugs and to focus on their beneficial roles and drug targets in cancer therapy and chemoprevention. Although their pharmacological mechanisms and biochemical roles in cancer biology and tumor chemoprevention are not fully understood, crude drugs are believed to have nutriceutical effects upon cancer patients.

Keywords: Crude drug, cancer, inflammation, cell cycle, apoptosis

Introduction of crude drugs

Throughout the history of medicine, many effective drugs were derived from natural extracts of plants or animals. For example, the anti-malarial drug- quinine is extracted from the bark of the cinchona tree. This fact might suggest to us that more primary anticancer drugs could well be found in nature. In the East since ancient times, especially in China and Korea, people have been using plant rhizomes, leaves or barks and other natural materials soaked in alcohol or wine as drugs to treat illness. These drugs that come from plants are called crude drugs.

Signaling the importance of drugs from natural origins is the growing evidence that indicates that diets rich in vegetables and fruits can reduce the risk of a number of chronic diseases, including cancer, cardiovascular diseases, diabetes, etc [1, 2]. Thus, as cancer incidence is on the rise, and cancer treatment still lacks effective drugs without significant side effects, the exploration of crude drugs has become more important. Fortunately, molecular biology and biochemical technology development has promoted research on crude drugs. New purification and analysis technologies have enabled crude drugs to be manufactured and made available for widespread use [3], and have achieved conspicuous success in tumor treatment and cancer biology research [3]. Crude drugs may act as treatments themselves, or their effective elements may be used for cancer treatment directly or as supplemental applications in the clinic. Additionally, crude drugs are used as a basis to screen for better anti-cancer drug precursors or in other ways that serve scientists in cancer research as pro-drugs.

Examples of crude drugs as anticancer agents

Beneficial effects of crude drugs are believed to be attributed to plant phytochemicals (various

factors in plant foods), such as carotenoids, antioxidative vitamins, phenolic compounds, terpenoids, steroids, indoles, and fibers, etc [3]. These are the effective elements considered to be responsible for reducing cancer risk. Below we cite several examples of phytochemicals that are used or have the potential for use in cancer treatment.

Paclitaxel

Paclitaxel (Taxol), shown in **Figure 1A**, is an effective and commonly used cancer drug approved for treating a variety of cancers, and it is under evaluation for the treatment of Alzheimer's disease and coronary heart disease also. As such, it is a crude drug success story. Isolated from the bark of the slow growing and endangered Pacific yew- *Taxus brevifolia* (from the tree family *Taxacae*), paclitaxel is considered a terpenoid, a member of a natural organic family of chemicals. It was first extracted from the Yew tree in the US in 1971 and, by 1992, received approval from the US Food and Drug Administration (FDA) for clinical use. Today, paclitaxel has proved effective for the treatment of many types of cancers, such as ovarian [1, 2, 4, 5], breast [1, 5, 6], lung [7, 8], esophageal [9], and liver cancers [10]. Unique activities of paclitaxel are that it binds to β-tubulin in the microtubule specifically and reversibly with a stoichiometry of almost one (relative to the α,β-tubulin dimer) [11, 12], inhibits cell division, blocks cell mitosis, stabilizes cytoplasmic microtubules, and induces the formation of the characteristic microtubule bundles in cells [13].

Curcumin

Other than paclitaxel (Taxol), quite a few natural compounds from fruit and vegetables are being investigated for its potential medicinal qualities. For example, curcumin (from the plant *Curcuma longa*) as shown in **Figure 1B**, used in Chinese medicine and in the Indian traditional food of curry as the yellow coloring agent in turmeric, is known for its antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and potentially combat various other disorders including diabetes, allergies, arthritis, and Alzheimer's disease [14]. Goel et al. [15] reported on curcumin and posited that because most cancers are caused by dysregulation of as many as 500 different genes, agents, such as curcumin, that target multiple genes are needed for the prevention and treatment of cancer. In studies to date, curcumin has been shown to interact with a wide variety of proteins and modify their expression and activity. These proteins include inflammatory cytokines and enzymes, transcription factors, and gene products linked with cell survival, proliferation, invasion, and angiogenesis [15]. As of 2007, 22 Phase I or II cancer-related clinical trials [16] involving curcumin have been ongoing. Several of these trials indicate that curcumin is safe and may exhibit therapeutic efficacy. For example, curcumin has inhibited the spread of various tumor cells in culture, prevented carcinogen-induced cancers in rodents, and inhibited the growth of human tumors in xenotransplant or orthotransplant animal models either alone or in combination with chemotherapeutic agents or radiation [14]. Recent studies reported that curcumin decreased survival of RT4V6 and KU7 bladder cancer cells in part at least through increased DNA fragmentation and other parameters associated with apoptosis [17]. In addition, curcumin potentiated the effects of other drugs and cytokines in bladder cancer cells, an action observed in other studies [17-20]. What has been observed was that while curcumin alone had minimal effects on NF-κB in RT4V6 or KU7 cells, it inhibited NF-κB activation when that activation was induced by agents, such as gemcitabine, tumor necrosis factor-alpha (TNF-α), and cigarette smoke, that induce NF-κB. Investigators concluded that suppression of induced NF-κB by curcumin may play a role in sensitizing bladder cancer cells and other cancer cell lines to various chemotherapeutic agents [17]. What has also been observed is that, possibly by inducing apoptosis and decreasing the expression of pro-apoptotic protein survival and the angiogenic proteins vascular endothelial growth factor (VEGF) and VEGF receptor 1 (VEGFR1), curcumin inhibited 253JB-V and KU7 bladder cancer cell growth in an animal model [21]. Details of curcumin's anticancer mechanisms that qualify it as a potential multi-targeted cancer therapeutic agent can be found in [14].

Another anticancer effect of curcumin was observed in an unpublished Phase II study at MD Anderson Cancer Center in which 25 pancreatic cancer patients were monitored while taking curcumin and no other treatment. A 73% tumor reduction was observed in one patient while on curcumin (it did grow back one month later).

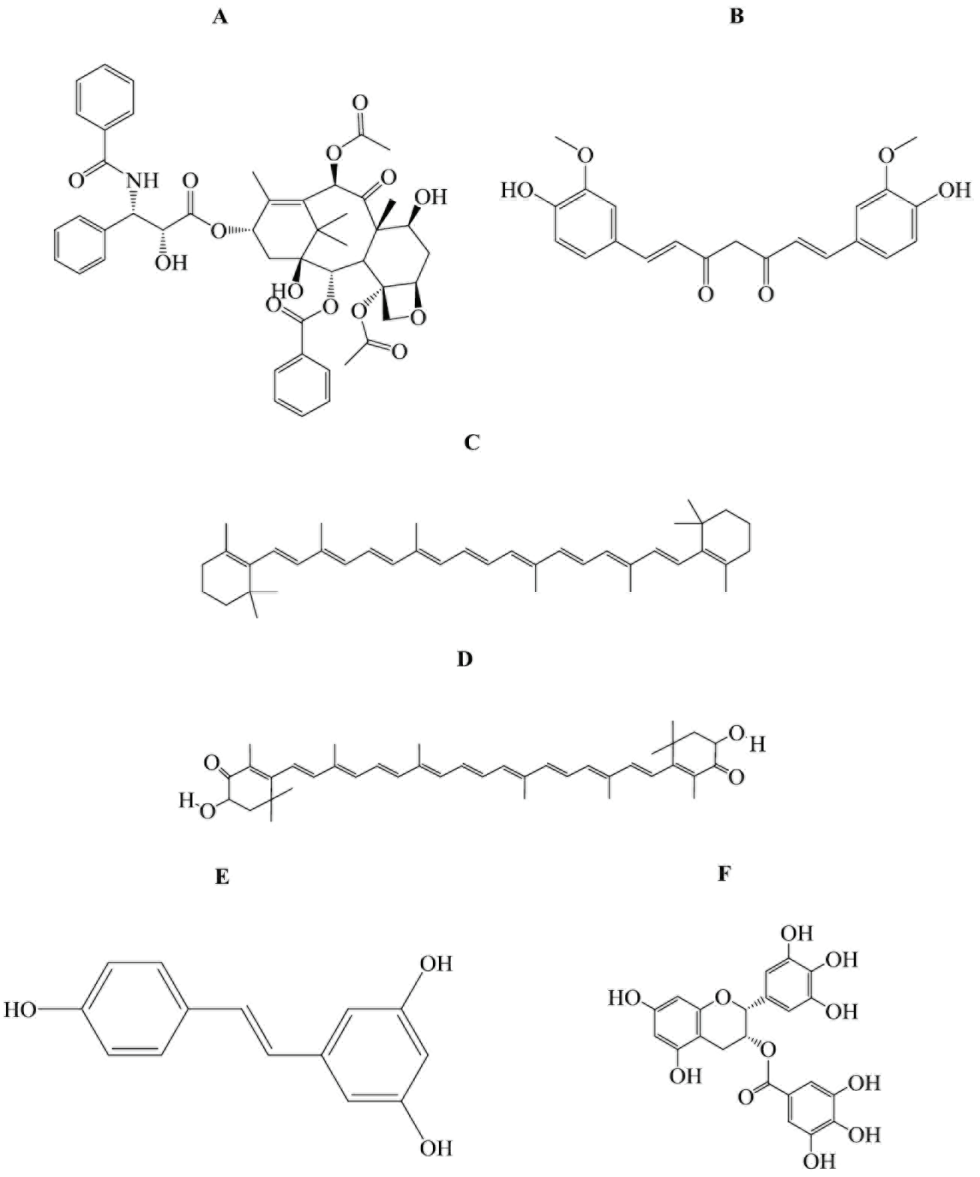

Figure 1. Chemical structures of some crude drug key elements. (**A**) Taxol; (**B**) Curcumin; (**C**) β-carotene; (**D**) Astaxanthin; (E) Resveratrol; (F) (-)-epigallocatechin-3-gallate (EGCG)

The disease in four patients stabilized (one patient lived 2.5 years longer than predicted) [14]. Other research provides support for the anticancer activity of curcumin in a wide variety of tumors including colon [11, 21, 22], pancreas [16], bladder [23, 24], and breast cancer [25].

Carotenoids

Similar to curcumin, carotenoids, found in nearly all brightly colored fruits and vegetables or seafood, have strong cancer-fighting properties. Their anticancer effect comes from their antioxidant properties. Antioxidants protect cells from free radicals, substances that work to destroy cell membranes and DNA. Contrary to popular belief, while the carotenoid β-carotene (**Figure 1C**) has a very high amount of vitamin A activity, not all carotenoids can be converted into vitamin A. As antioxidants, carotenoids have many benefits. For example, smokers tend to have higher concentrations of free radicals in their blood due to the chemicals they inhale. Studies suggest that antioxidants may lower a

smokers' risk of lung cancer [26, 27]. Studies also suggest that carotenoids may help to prevent prostate, breast [27-37], and skin [38, 39] cancer as well as endometrial cancer [37].

Astaxanthin (**Figure 1D**) is another carotenoid, found in salmon, red fish, shrimp and crab, which shows anti-carcinogenic effects in mouse lung and liver cancer models. In the HepG2 human liver cancer cell line, astaxanthin significantly inhibited, in a dose-dependent manner, the proliferation of liver cancer cells. Flow cytometric analysis demonstrated that astaxanthin restrained the cell cycle progression at G1 and induced apoptosis. Further examinations through real-time quantitative RT-PCR revealed that astaxanthin enhanced the expression of $p21^{CIP1/WAF1}$, GADD153 and c-myc genes, suggesting that astaxanthin will be a promising agent for use in chemoprevention or as a cancer therapeutic [3].

Polysaccharide

Oranges not only contain the carotenoid β-carotene that is responsible for their orange color, but also contain another anticancer agent, GCS-100, a polysaccharide derived from citrus pectin. In multiple myeloma cells, GCS-100 overcomes bortezomib resistance and enhances dexamethasone-induced apoptosis. In other words, even in the presence of bone marrow–derived stromal cells (BMSCs), GCS-100 inhibits the growth of multiple myeloma cells and even blocks VEGF-induced migration of the cells, suggesting anti-angiogenic activity [40]. GCS-100 also overcomes both the growth/survival advantage conferred by NF-κB and the cytoprotective effects of the antiapoptotic protein Bcl-2. Biochemically, GCS-100–induced apoptosis occurs predominantly via the caspase-8-to-caspase-3 signaling pathway; GCS-100 does not significantly alter mitochondrial apoptotic signaling, including alterations in DY_m, O_2^- production, or the activation of caspase-9. When combined with dexamethasone, low dose GCS-100 triggers additive anti-multiple myeloma activity via both the caspase cascade as well as through the inhibition of the anti-apoptotic protein Galectin [40].

Mushrooms

Another natural ingredient with potential as a crude drug, given its anti-tumor as well as antiviral, and antibacterial properties, is the mushroom. Studies to date report mushroom supplementation enhanced natural killer (NK) cell activity and IFN-γ and TNF-α production [41-43]. It increases IL-2 ($p = 0.09$) but not IL-10 production by splenocytes. Significant correlations were found between NK cell activity and production of IFN-γ ($r = 0.615$, $p < 0.001$) and TNF-α ($r = 0.423$, $p = 0.032$) in splenocytes. Mushroom supplementation did not affect macrophage production of IL-6, TNF-α, prostaglandin E(2), nitric oxide (NO), and H_2O_2, nor did it alter the percentage of total T cells, helper T cells (CD4(+)), cytotoxic or suppressive T cells (CD8(+)), regulatory T cells (CD4(+)/CD25(+)), total B cells, macrophages, or NK cells in spleens. These results suggest that increased intake of white button mushrooms may promote innate immunity against tumors and viruses through the enhancement of a key component, NK cell activity that is mediated through increased IFN-γ and TNF-α production [43, 44]. The effects of mushrooms are thought to be due to their ability to modulate immune cell functions [43]. These compounds from macromycetes fungi belong mainly to polysaccharides especially beta-d-glucan derivates, glycopeptide/protein complexes (polysaccharide-peptide/protein complexes), proteoglycans, proteins, and triterpenoids. Among polysaccharides, beta (1-->3)-d-glucans and their peptide/protein derivates, and other proteins- fungal immunomodulatory proteins (Fips) have an important role in immunomodulating and anti-tumor activities [44, 45].

Resveratrol

Another possible crude drug or crude drug element found in the skin of red grapes and, therefore, in red wine that has been identified on the basis of its ability to inhibit cyclooxygenase (COX) activity is resveratrol (**Figure 1E**). Resveratrol inhibits cellular events associated with tumor initiation, promotion, and progression. Further, it suppresses TNF-α-induced activation of nuclear transcription factors NF-κB, activator protein-1 (AP-1) and apoptosis, suggesting a potential role in reducing oxidative stress and lipid peroxidation [46-48].

Green tea

Like resveratrol in the skin of grapes, green tea is now well-known to most people for having medicinal benefit. Green tea polyphenol- (-)-epigallocatechin-3-gallate (EGCG) (**Figure 1F**) has various beneficial properties including che-

mopreventive, anticarcinogenic, and antioxidant actions [49]. One of EGCG's benefits is that it may cause cancer cells to die in much the same way as normal cells. In a recent study, the MAPKKK protein MEKK1, which plays a role in the JNK-mediated signaling pathway, also activates NF-κB via activation of IKKβ. Dysregulation of the NF-κB pathway plays an important role in the development of various types of cancer [50-52]. EGCG inhibited a tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced DNA binding of NF-κB and CREB in mouse skin *in vivo*. EGCG also suppressed TPA-induced phosphorylation and subsequent degradation of IκBα, and prevented nuclear translocation of p65 [53]. EGCG has been reported to exert an anti-inflammatory effect in endothelial cells by controlling monocyte chemotactic protein-1 (MCP-1) expression, at least in part, mediated through the suppression of p38 and NF-κB activation [54]. EGCG has been shown to be helpful in regulating mast-cell-mediated allergic inflammatory response by inhibiting the production of TNF-α, IL-6, and IL-8 through the inhibition of the intracellular Ca^{2+} level, ERK1/2, and NF-κB activation [55]. EGCG markedly inhibited IL-1β-mediated IL-1β-receptor-associated kinase (IRAK) degradation and the signaling events downstream from IRAK degradation such as IKK activation, IκBα degradation, and NF-κB activation. In addition, EGCG inhibited phosphorylation of the p65 subunit of NF-κB. The functional consequence of this inhibition was evident by inhibition of IL-8 gene expression [56]. It has been reported that EGCG-induced apoptosis in human prostate carcinoma LNCaP cells by negative regulation of NF-κB activity, thereby decreasing the expression of the proapoptotic protein Bcl-2 [57].

The natural ingredients of curcumin, carotenoids, mushrooms, EGCG in green tea, resveratrol in red grape skin, and GCS-100 in citrus pectin are only some of the natural ingredients that can, like paclitaxel (Taxol), become crude drugs with potential multi-targeting efficacy in fighting cancer. Below we detail a few other ingredients with similar potential: the herbal elements *Scutellaria baicalensis* and *Artemisia asiatica* as well as red and white ginseng extract, isoliquiritigenin in licorice and capsaicin in hot chili peppers.

Herbals

Scutellaria baicalensis is a widely used Chinese herbal medicine historically used as anti-inflammatory and anticancer therapy that is being tested as a treatment for prostate cancer. Two human prostate cancer cell lines (LNCaP, androgen dependent, and PC-3, androgen independent) were assessed for growth inhibition when exposed to *S. baicalensis*. *S. baicalensis* exerted dose- and time-dependent increased growth inhibition in both cell lines. After treatment with *S. baicalensis*, PGE2 synthesis in both cells was significantly reduced, resulting from direct inhibition of COX-2 activity rather than COX-2 protein suppression. *S. baicalensis* also inhibited prostate-specific antigen production in LNCaP cells. Finally, *S. baicalensis* suppressed expression of cyclin D1 in LNCaP cells, resulting in a G1 phase arrest, while inhibiting cdk1 expression and kinase activity in PC-3 cells, ultimately leading to a G2/M cell cycle arrest. In animal studies, after a 7-week treatment period with *S. baicalensis,* tumor volume was reduced by 50%, demonstrating that *S. baicalensis* may be a novel anticancer agent for treating prostate cancer [58].

Artemisia asiatica has also been frequently used in traditional Asian medicine for the treatment of diseases involving inflammation, cancer, and microbial infection. An extract of *A. asiatica*, DA-9601, with ethanol, blocked TNF-α-mediated inflammatory signals by potentially modulating the p38 kinase pathway and/or a signal leading to NF-κB-dependent pathways in gastric epithelial cells [59].

Another potential crude drug or crude drug element are red and white ginseng extract. Oral administration of red ginseng extracts (1% in diet for 40 weeks) in C3H/He male mice resulted in the significant suppression of spontaneous liver tumor formation. The average number of tumors per mouse in the control group and in the red ginseng extracts-treated group was 1.06 and 0.33 ($p < 0.05$), respectively. Incidence of liver tumor development was also lower in red ginseng extracts-treated group, although the difference from control group was not statistically significant. Like red ginseng extracts, white ginseng extracts have also shown anti-carcinogenic activity that is being investigated. In an ongoing study, the administration of white ginseng extracts was proven to suppress tumor promoter-induced phenomena in vitro and in vivo. Interestingly, oral administration of a white ginseng-containing Chinese medicinal prescription known as ren-shen-yang-

Table 1. Crude drugs or elements of crude drugs in various research and clinical phases

Crude drugs	Status	Targets
Paclitaxel (Taxol)	In FDA-approved clinical use	β-tubulin
Curcumin	In Phase I/II clinical trials	Multiple targets
Astaxanthin	In pre-clinical research phase	$p21^{CIP1/WAF}$, GADD153, c-myc
Citrus pectin	In pre-clinical research phase	NF-κB
Mushroom	In pre-clinical research phase	CD4 ,CD8, CD25, IFN-γ, IL-6, TNF-α
Resveratrol	In pre-clinical research phase	NF-κB
EGCG	In pre-clinical research phase	VEGF, NF-κB, IKKβ, IκB-α
Scutellaria baicalensis	In pre-clinical research phase	COX-2, cyclin D1
Artemisia asiatica	In pre-clinical research phase	p38, NF-κB
Red ginseng	In pre-clinical research phase	CD-1
Isoliquiritigenin	In pre-clinical research phase	$p21^{CIP1/WAF1}$
Capsaicin	In pre-clinical research phase	Bcl-2

rong-tang, resulted in the suppression of skin tumor promotion by 12-o-tetradecanoylphorbol-13 acetate in 7,12-dimethylbenz[a] anthracene-initiated CD-1 mice, suggesting the usefulness of ginseng in the field of cancer prevention [60].

Isoliquiritigenin is a natural flavonoid isolated from licorice, shallot and bean sprouts that has significantly inhibited, in a dose- and time-dependent manner, the proliferation of cancer cells in the A549 human lung cancer cell line. Flow cytometric analysis demonstrated that isoliquiritigenin restrained the cell cycle progression at G2/M phase. Further examinations using cDNA arrays and real-time quantitative RT-PCR revealed that isoliquiritigenin enhanced the expression of $p21^{CIP1/WAF1}$, a universal inhibitor of cyclin-dependent kinases (CDKs). These results suggest that isoliquiritigenin will be a promising agent for use in chemoprevention or therapeutics against lung cancer [61].

A pungent ingredient of hot chili peppers- capsaicin (8-methyl-N-vanillyl-6-nonenamide), has been reported to possess substantial anti-carcinogenic and anti-mutagenic activities; it can induce apoptosis in highly metastatic B16-F10 murine melanoma cells and, in a concentration-dependent manner, inhibit their growth. A pro-apoptotic effect of capsaicin was also evidenced by nuclear condensation, internucleosomal DNA fragmentation, in situ terminal nick-end labeling of fragmented DNA (TUNEL), and an increased sub G1 fraction. Treatment of B16-F10 cells with capsaicin caused, in a dose-dependent manner, a release of mitochondrial cytochrome c, activation of caspase-3, and cleavage of poly (ADP-ribose) polymerase. Furthermore, Bcl-2 expression in the B16-F10 cells was slightly down-regulated by capsaicin treatment. In contrast, there were no alterations in the levels of Bax in capsaicin-treated cells. Collectively, these findings indicate that, via down-regulation of the Bcl-2, capsaicin induces apoptosis of B16-F10 melanoma cells [62].

Concluding remarks

The above excerpts show a representative sample of promising natural elements, including Paclitaxel (Taxol), curcumin, β-carotene, astaxanthin, citrus pectin, mushroom, resveratrol, EGCG, *Scutellaria baicalensis, Artemisia asiatica,* red and white ginseng extracts, isoliquiritigenin, and capsaicin, that are being used and tested as crude drugs or elements of crude drugs in research and in the clinic (**Table 1**). Crude drugs have a wide range of effects on oncogenes, cell signaling and apoptosis ($p21^{CIP1/WAF1}$, GADD153, c-myc, COX-2, NF-κB, CDK1, p38, and Bcl-2, etc.) that may be potential therapeutic targets for cancer. Crude drugs are not new. To date, crude drugs have displayed an important role in the development of new anticancer drugs. However, evaluation of crude drugs up until now has been narrowly focused on the plants and seafood. We should broaden our vision and expand our scope to

also include insect and mineral derived therapies. Eastern medicine has a long tradition of using scientific methods involving natural active constituents as forerunner compounds and then through organic synthesis and structural transformation finding new drugs or combining natural compounds with therapeutic effect. As the results of the previous investigations show, natural ingredients have vast potential for treating cancer with potentially fewer side effects than most of today's cancer therapies. Moreover, receptor-based therapeutics is just one avenue of investigation for these new therapies. Crude drugs or their active ingredients may have diverse mechanisms of action. By increasing research into crude drugs, we hope to identify the most promising agents and understand their many actions. Ultimately we hope to tap the vast potential of this class of agents and improve cancer therapy.

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