Targeting apoptosis pathways in cancer with magnolol and honokiol, bioactive constituents of the bark of *Magnolia officinalis*

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ABSTRACT: Magnolol and honokiol, main active compounds from the bark of *Magnolia officinalis*, have been found to have various pharmacological actions, including anti-oxidative, anti-inflammatory, anti-tumor, and anti-microbial properties, without appreciable toxicity. Recently, the anti-tumor activity of magnolol and honokiol has been extensively investigated. Magnolol and honokiol were found to possess anti-tumor activity by targeting the apoptosis pathways, which have been considered as targets for cancer therapies. This review will focus on the mechanisms by which magnolol and honokiol act on apoptosis pathways in cancer that have been characterized thus far, including the death receptor-mediated pathway, mitochondria-mediated pathway, caspase-mediated common pathway, and regulation of apoptosis-related proteins. These breakthrough findings may have important implications for targeted cancer therapy and modern applications of traditional Chinese medicine.

Keywords: Anti-tumor activity, apoptosis pathways, honokiol, magnolol, *Magnolia officinalis*

1. Introduction

Apoptosis is a normal physiological process that plays an important role in many normal functions ranging from embryonic development to adult tissue homeostasis (1). Defects in apoptosis are common phenomena in many types of cancer and are also the critical step in tumorigenesis and resistance to therapy (2). Thus, apoptotic pathways have been considered as targets for cancer therapies (3).

Traditional Chinese medicine (TCM) has held and still holds an important position in primary health care in China and has recently been recognized by Western countries as a fertile source of novel lead molecules as part of modern drug discovery. Although TCM has been used for thousands of years in China, its mechanisms of healing at the molecular level are still largely unknown. To better understand the therapeutic action of TCM, considerable efforts have been made to identify the principal constituents of TCM and to unravel the molecular mechanisms behind the efficacy observed (4). Over the last two decades, more and more bioactive compounds have been identified from TCM herbs. Magnolol and honokiol, main active compounds from the bark of *Magnolia officinalis* (Cortex Magnoliae Officinalis), have been found to possess anti-tumor activity by inducing apoptosis in cancer (5). This review will focus on the mechanisms by which magnolol and honokiol act on apoptosis pathways in cancer that have been characterized thus far. Due to space limitations, only key studies are cited.

2. Magnolol and honokiol

The Chinese herb *Magnolia officinalis* is widely used as a folk remedy for gastrointestinal disorders, cough, anxiety, and allergic diseases as an oriental medicine in South Korea, China, and Japan (6). Magnolia bark is rich in two biphenol compounds, magnolol (5,5'-diallyl-2,2'-dihydroxybiphenyl, C₁₈H₁₈O₂) and honokiol (3,5'-diallyl-4,2'-dihydroxybiphenyl, C₁₈H₁₆O₂), that have been extensively investigated (7,8). The structures of magnolol and honokiol are shown in Figure 1. The magnolol content of magnolia bark is generally in the range of 2-10 percent, while honokiol tends to occur naturally at 1-5 percent in dried magnolia bark (9). The potent activity of honokiol and magnolol appears to be due to the presence of hydroxyl and allylic groups on a biphenolic moiety (10).
Magnolol, a hydroxylated biphenyl compound isolated from the stem bark of *Magnolia officinalis*, is commonly used to treat acute pain, cough, anxiety, and gastrointestinal disorders in East Asia (11). Various pharmacological actions have been reported for magnolol, including anti-inflammatory activity, antimicrobial activity (12), antiperoxidative activity (13), anti-coagulatory activity, anti-oxidant activity (14), neuroprotective activity (15), antitumor action (16-18), alleviation of inflammatory pain (19), and protection of cortical neuronal cells from chemical hypoxia (20).

Honokiol, a magnolol isomer, differs in the relative arrangement of one of its hydroxyl groups with respect to allyl groups in the phenolic ring (21) and is the most important bioactive constituent within magnolia bark studied thus far. Honokiol has also been found to have a variety of pharmacological action, such as anti-inflammatory action (22), antithrombotic activity (23), anti-arrhythmic activity (24), neuroprotective activity (15), antioxidative action (25), and anxiolytic action (26). Numerous animal studies have also demonstrated that honokiol acts as an anti-stress agent and a potent suppressor of oxidative damage and cancer (27).

Recently, magnolol and honokiol have been reported to have antitumor action by inhibiting proliferation, inducing apoptosis and differentiation, countering metastasis, suppressing angiogenesis, and reversing multidrug resistance (10,28,29). Numerous signaling pathways have been implicated in the regulation of apoptosis by magnolol and honokiol (30).

### 3. Targeting apoptosis pathways in cancer with magnolol and honokiol

Apoptosis occurs through two main pathways (31,32). The first, referred to as the extrinsic or death receptor pathway, involves ligation of death receptors (e.g. Fas (CD95), tumor necrosis factor receptors (TNFR), and TNF-related apoptosis-inducing ligand (TRAIL) receptors) with their ligands resulting in a sequential activation of caspase-8 and -3. The second pathway is the intrinsic or mitochondrial pathway in which intrinsic death stimuli (e.g. reactive oxygen species (ROS), DNA-damaging reagents, and Ca^{2+} mobilizing stimuli), directly or indirectly activate the mitochondrial pathway, resulting in the release of cytochrome c and the formation of the apoptosome complex consisting of cytochrome c, Apaf-1, and caspase-9 (Figure 2). Caspase-9 is activated at the apoptosome and in turn activates caspase-3. Between the death receptor and the mitochondrial signaling pathways, the pro-apoptotic protein Bid serves as a cross-talker upon cleavage by activated caspase-8 by inducing the translocation of the pro-apoptotic proteins Bax and/or Bak to the mitochondrial membrane (33). Both pathways converge to a final common pathway involved in the activation of a cascade of proteases called caspases that cleave regulatory and structural molecules, culminating in the deaths of cells (Figure 2). Although understanding of the detailed signaling pathways that trigger apoptosis is incomplete, this process is controlled by a number of complex proteins that are activated by various triggers and arranged in sequential signaling modules. In the receptor-mediated pathway, FLICE-inhibitory protein (c-FLIP) and XIAP negatively regulate the activity of caspase-8 and caspase-3, respectively (31,32). In the mitochondria pathway, apoptosis is largely controlled by the pro-apoptotic proteins, e.g. Bax, Bak, Bid, and Smac, and the anti-apoptotic proteins, e.g. Bcl-2, Bcl-xL, Mcl-1, and XIAP (3).

Many studies have shown that magnolol and honokiol induce the apoptosis of various tumor cells. Magnolol induces the apoptosis of many human cancer cell lines, including lung squamous cancer CH-27 cells, HL-60 cells, colon cancer COLO 205 cells, and liver cancer HepG2 cells (34-38), but does not induce the apoptosis of bovine aorta endothelial BAE cells (38) or polymorphonuclear and mononuclear leukocytes (35). Honokiol induces the apoptosis of human lymphoid leukemia Molt 4B cells, CH27 cells, B-CLL cells, and RKO cells in a time- and dose-dependent manner (5,34,39,40). In addition, honokiol has a more obvious apoptosis-inducing effect on B-CLL cells than on normal mononuclear leukocytes (40). *In vivo*, honokiol was highly effective against SVR angiosarcoma (41) and breast cancer in nude mice (42) and in a human A549 lung cancer xenograft model (43) with the increased induction of apoptosis.

This review will focus on the mechanisms by which magnolol and honokiol act on apoptosis pathways in cancer that have been characterized thus far, including the death receptor-mediated pathway, mitochondria-mediated pathway, caspase-mediated common pathway, and regulation of apoptosis-related proteins.
apoptosis (44). Activation of the death receptor-mediated apoptotic pathway is primarily inhibited by cellular c-FLIP, which inhibits caspase-8 activation by preventing recruitment of caspase-8 to the death-inducing signaling complex. In some cells, the activation of caspase 8 may be the only requirement for death to ensue, while in other cell types caspase 8 interacts with the intrinsic apoptotic pathway by cleaving Bid (a proapoptotic member of the Bcl-2 family), leading to the subsequent release of cytochrome c (45).

Figure 2. Effects of magnolol (M) and honokiol (H) on extrinsic (also called receptor-mediated) and intrinsic (also called mitochondria-mediated) apoptosis pathways in cancer. The extrinsic pathway involves ligation of death receptors with their ligands, resulting in a sequential activation of caspase-8 and -3. Intrinsic death stimuli, e.g. ROS, DNA-damaging reagents, or Ca²⁺ mobilization directly or indirectly activates the mitochondrial pathway by inducing release of cytochrome c and formation of the apoptosome, which consists of Apaf-1 and caspase-9. Caspase-9 is activated at the apoptosome and in turn activates pro-caspase-3.
Studies have shown that activation of the Fas-mediated pathway did not always result in magnolol-induced apoptosis. In response to magnolol administration, Fas was activated and cytochrome c was translocated from mitochondria to the cytoplasm through elevation of the cytosolic free Ca$^{2+}$ concentration and downregulation of Bcl-2. Caspase-8 was activated by Fas activation, whereas caspase-9 was activated by cytochrome c release (46). Pretreating cells with ZB4 (which disrupts the Fas response mechanism) also decreased subsequent magnolol-induced caspase-8 activation and reduced the occurrence of apoptosis (46). Whether magnolol activates Fas directly or it promotes the action of a Fas ligand that in turn activates Fas remains to be determined.

Honokiol down-regulated c-FLIP in cancer cells, resulting in sensitization of cancer cells to both TRAIL-mediated and Fas ligand-mediated apoptosis (47). Honokiol alone moderately inhibited the growth of human lung cancer cells; when combined with TRAIL, however, honokiol had a greater impact on decreasing cell survival and inducing apoptosis than did TRAIL alone, indicating that honokiol cooperates with TRAIL to enhance apoptosis. This was also true for Fas-induced apoptosis when it was combined with a Fas ligand or an agonistic anti-Fas antibody. Of several apoptosis-associated proteins tested, c-FLIP was the only one that was rapidly down-regulated by honokiol in all of the cell lines tested (47). These results indicate that c-FLIP down-regulation is a key step in honokiol’s modulation of death receptor-induced apoptosis.

3.2. Targeting cancer cells by mitochondria-mediated apoptosis

The effects of magnolol on the intrinsic pathway of apoptosis have been examined in many cell lines, including human leukemia U937 cells (48), human hepatoma Hep G2 and colon cancer COLO 205 cells (46), and rat vascular smooth muscle cells (VSMCs) (49). Magnolol increased caspase-3 and caspase-9 activity significantly and reduced the mitochondrial potential ($\Delta\Psi_m$) in these cells. Treatment with magnolol was found to partly inhibit growth by inducing apoptosis in cultured human leukemia U937 cells and apoptosis was found to be induced via the sequential ordering of molecular events. Thus, magnolol-induced apoptosis is mediated via the intrinsic pathway with release of AIF from mitochondria in U937 cells (48). Lin SY, et al. showed that treatment with magnolol induced apoptosis by increasing translocation of cytochrome c from mitochondria to cytosol and activation of caspase-3, -8, and -9 in cultured Hep G2 and COLO 205 cell lines (46). In addition, Huang SH, et al. showed that magnolol initiated apoptosis via cytochrome c/caspase-3/PARP/AIF and PTEN/Akt/caspase-9/PARP pathways and necrosis via PARP activation (50).

Similar results were found in honokiol-treated cells. Honokiol treatment caused the release of mitochondrial cytochrome c to cytosol and sequential activation of caspases in human squamous lung cancer CH27 cells (51). Honokiol also induced release of mitochondrial proapoptotic protein AIF to the cytosol in human multiple myeloma (MM) cells (52). The current review has mainly focused on induction of mitochondria-mediated apoptosis via reactive oxygen species (ROS)-mediated and Ca$^{2+}$-mediated mechanisms of magnolol and honokiol.

3.2.1. ROS-mediated mechanisms

ROS, including free radicals such as superoxide (•O$_2^-$), hydroxyl radicals (•OH), and the non-radical H$_2$O$_2$, are generated through multiple sources in the cells (53). Tumors, and particularly those in advanced stages, produce elevated levels of ROS and have an altered redox status. ROS and mitochondria play an important role in apoptosis induction under both physiological and pathological conditions (54). Interestingly, mitochondria are both sources and targets of ROS. Cytochrome c release from mitochondria, which triggers caspase activation, appears to be largely mediated by direct or indirect ROS action (35). High levels of ROS may cause the oxidative damage of various cellular components and finally result in cell apoptosis.

Magnolol has been shown to attenuate oxidized low-density lipoprotein (oxLDL)-induced ROS generation, subsequently reducing nuclear factor-kappaB (NF-$\kappa$B) activation (56). Magnolol also inhibited UV-induced mutations by scavenging •OH generated by UV irradiation (57). The attenuation of ROS by magnolol has been proposed as a reason for its inhibitory effect on neutrophil adherence to the extracellular matrix during injury (58).

Honokiol was also found to be a potent scavenger of hydroxyl radicals, which is likely due to its allyl groups (22,59). The ortho allyl group may potentially form a six-member ring after absorption of a hydroxyl group. This may account for its superior antioxidant activity when compared to magnolol, which has two allyl groups with hydroxyl groups in the para position and thus cannot form a six-member ring. Honokiol-induced apoptosis has been closely associated with ROS production. Inhibition of reactive oxygen-driven tumors by honokiol is due to its involvement in the NADPH oxidase (NOX) pathway (22). This inhibition was first demonstrated in neutrophils (22) and later in hepatocytes (60) and human umbilical vein endothelial cells (HUVECs) (22). A possible chemical mechanism for this involves a peroxide intermediate followed by the phenolic hydroxyl group attacking the peroxide carbon chain, yielding a pentose or hexose ring and water.

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3.2.2. \(Ca^{2+}\)-mediated mechanisms

\(Ca^{2+}\) signals are known to play an important role in the regulation of cell death and survival (61). One known \(Ca^{2+}\)-regulated Bel-2-associated pro-apoptotic protein is Bad. In non-apoptotic cells, Bad is phosphorylated and sequestered by the cytosolic protein 14-3-3, avoiding its hetero-dimerization with Bel-2 and Bel-xL at the mitochondrial membrane. In the presence of an apoptotic stimulus (e.g. \(Ca^{2+}\)), Bad is dephosphorylated by \(Ca^{2+}\)/calmodulin-dependent phosphatase calcineurin, leading to dissociation from its inhibitor 14-3-3 and promoting apoptosis (62). Since mitochondria are the major organelles that take up \(Ca^{2+}\), \(Ca^{2+}\) over-loading of the mitochondria may also directly lead to release of cytochrome c as part of a stress response.

Lin SY, et al. showed that treatment with \(100 \mu M\) of magnolol increased cytosolic free \(Ca^{2+}\), resulting in induced apoptosis in cultured human Hep G2 and COLO 205 cell lines but not in human untransformed gingival fibroblasts and human umbilical vein endothelial cells (46). In rat neutrophils, magnolol increased \([Ca^{2+}]\), by stimulating \(Ca^{2+}\) release from internal stores and \(Ca^{2+}\) influx across the plasma membrane in a concentration-dependent manner via the inositol trisphosphate signalling pathway (63). Magnolol relaxed vascular smooth muscle by releasing endothelium-derived relaxing factor (EDRF) and by inhibiting calcium influx through voltage-gated calcium channels (64). Magnolol also increased the probability of these channels opening in a concentration-dependent manner, independent of internal \(Ca^{2+}\), in tracheal smooth muscle cells (65).

3.3. Targeting cancer cells by caspase-mediated apoptosis

The caspases are a family of proteins that are one of the main executors of the apoptotic process. As of November 2009, twelve caspases have been identified in humans (66). There are two types of apoptotic caspases: initiator (apical) caspases (caspase-2, -8, -9, and -10) and effector (executioner) caspases (caspase-3, -6, and -7). Initiator caspases cleave inactive pro-forms of effector caspases, thereby activating them. Effector caspases in turn cleave other protein substrates within the cell, triggering the apoptotic process.

Activation of caspase-3, -8, -9, and -2, and the proteolytic cleavage of poly(adenosine diphosphate-ribose) polymerase (PARP) were noted during apoptosis induced by magnolol (46). Pretreatment with Z-Val-Ala-Asp-fluoromethyl ketone (Z-VAD-FMK), a pan-caspase inhibitor, markedly inhibited magnolol-induced cell death but did not prevent cytosolic cytochrome c accumulation. Apoptosis may be partially attenuated by caspase-3 and -2 inhibitors. These results indicate that magnolol-induced apoptotic signaling was carried out through mitochondrial alterations to caspase-9 and that the downstream effector caspases were then activated sequentially (35).

Honokiol-induced apoptosis is characterized by the activation of caspase-3, -8, and -9 and cleavage of PARP (48). Honokiol induced caspase-dependent cell death in all of the B-CLL cells examined and was more toxic toward B-CLL cells than to normal mononuclear cells, suggesting that malignant cells were more susceptible. Although activation of caspase-3, -8, and -9 is triggered by honokiol, the pan-caspase inhibitor Z-VAD-FMK does not abrogate honokiol-induced apoptosis (52). Importantly, honokiol treatment induces the release of an executioner of caspase-independent apoptosis, AIF, from mitochondria. Honokiol also induced apoptosis in the SU-DHL4 cell line, which has low levels of caspase-3 and -8 (52). These results suggest that honokiol induced apoptosis via both caspase-dependent and -independent pathways.

3.4. Targeting cancer cells by regulating apoptosis-related proteins

Treatment with magnolol significantly increased the expression of Bad and Bel-x(S) proteins, whereas it decreased the expression of Bel-x(L) (67). Magnolol treatment also caused a decrease in Ser(136) phosphorylation of Bad, which is a downstream target of Akt, and translocation of Bax to the mitochondrial membrane. Similar results were observed in the human colon cancer HCT116Bax(+/-) cell line but not in the HCT116Bax(-/-) cell line. In addition, apoptotic cell death due to magnolol was found to be associated with significant inhibition of pEGFR, pPI3K, and pAkt (67).

Honokiol-induced apoptosis correlated with induction of Bax, Bak, and Bad and a decrease in Bel-xL and Mel-1 protein levels. Transient transfection of PC-3 cells with Bak- and Bax-targeted siRNAs and Bel-xL plasmid conferred partial yet significant protection against honokiol-induced apoptosis (68). Another study showed that honokiol caused cleavage of Mel-1 and downregulation of XIAP while Bad was markedly upregulated; Bid, p-Bad, Bak, Bax, Bel-2, and Bel-xL were unchanged (52). Honokiol also induced release of mitochondrial proapoptotic protein AIF to the cytosol and prevented phosphorylation of Akt, Stat-3, and Erk2, again implying an upstream target of action (52,69).

The effects of magnolol and honokiol on two important apoptosis-related proteins, p53 and NF-kB, have been summarized below.

3.4.1. p53

Loss of function of the p53 tumor suppressor gene is a frequent and important event in the genesis or progression of many human malignancies. In many tumor cells, wild-type p53 is thought to participate
in apoptosis in response to DNA damage (70). P53 may transactivate apoptotic regulators, such as Bcl-2, and Bach (75-77). Recent studies have shown that p53 plays a role in apoptosis by the mitochondria-mediated apoptotic pathway (74,78). Activation of p53 upregulates Bach, increases the ratio of Bach:Bcl-2, and releases cytochrome c and other polypeptides from the intermembrane space of mitochondria into the cytoplasm (76). P53-dependent apoptosis was activated by the Bach/mitochondrial/caspase-9 pathway.

Honokiol has been found to prevent the growth of MDA-MB-231 breast cancer cells in murine xenografts (79). An interesting finding is that MDA-MB-231 cells display mutant p53 and mutant K-ras, which is preferentially observed in the triple-negative breast cancer phenotype (79,80). In the same study, honokiol had less activity on the MCF7 breast cancer cell line, which exhibited wild-type p53 and loss of p16ink4a. Given that SVR cells have defects in p53 signaling because of expression of SV40 large T and that MDA-MB-231 cells also express mutant p53, tumors that have defects in p53 signaling may be targets of honokiol. Similarly, honokiol caused apoptosis in other solid-tumor cell lines that feature mutant p53 and ras activation, including lung and bladder cell lines (81). Thus, honokiol appears to have distinct activity against tumors with mutant p53, through its inhibition of ras-phospholipase D activation, and tumors with wild-type p53, through its induction of cyclophilin D. However, Wang T, et al. showed that honokiol induced RKO cell apoptosis by activating the caspase cascade via a p53-independent pathway (82). Hahm ER, et al. also showed that exposure of human prostate cancer cells (PC-3, LNCaP, and C4-2) to honokiol resulted in apoptotic DNA fragmentation in a concentration- and time-dependent manner, irrespective of their androgen responsiveness or p53 status (88).

3.4.2. NF-κB

The NF-κB pathway is one of the most important cellular signal transduction pathways involved in immunity, inflammation, proliferation, and defense against apoptosis (83). NF-κB is generally considered to be a survival factor that activates expression of various anti-apoptotic genes, e.g. Bcl-2, Bcl-xL, Mcl-1 and c-FLIP, that block apoptosis (83,84). The classic form of NF-κB is the p65/p50 heterodimer that contains the transcriptional activation domain and is sequestered in the cytoplasm as an inactive complex by IκB. Acute stimuli such as TNF-α, LPS or PMA lead to the activation of IκB kinases (IKK), which in turn phosphorylate Ser32 and Ser36 within the N-terminal response domain of IκB. Phosphorylated IκB undergoes ubiquitination-dependent proteolysis and the release of IκB unmask the nuclear localization signal and results in the translocation of NF-κB to the nucleus, followed by the activation of specific target genes.

Both magnolol and honokiol have been shown to inhibit the NF-κB signaling pathway. In a previous study, magnolol was shown to reduce the nuclear NF-κB content in TNF-α-stimulated endothelial cells (85). However, their mechanisms of action are poorly understood. Chen YH, et al. demonstrated that magnolol suppressed IKK activity, stabilized cytoplasmic IκBα, and subsequently reduced the nuclear translocation and phosphorylation of the p65 subunit of NF-κB (86). Magnolol also inhibited NF-κB-dependent reporter gene expression induced by TNF-α and it inhibited over-expression of NIK, IKK, and the p65 subunit while it enhanced TNF-α-mediated apoptosis. In human U937 promonocyes cells, magnolol inhibited the TNF-α-stimulated phosphorylation and degradation of the cytosolic NF-κB inhibitor IκBα and did so in a dose-dependent manner (87). In addition, magnolol differentially down-regulated the expression of NF-κB-regulated inflammatory gene products, e.g. MMP-9, IL-8, MCP-1, MIP-1α, and TNF-α. The involvement of IKK was further verified in a HeLa cell NF-κB-dependent luciferase reporter system (87).

Honokiol affected NF-κB signaling, but not through a direct effect on NF-κB DNA binding (88). Honokiol inhibited TNF-induced NF-κB activation and IκBα phosphorylation and degradation through its inhibition of the activation of IκB kinase and Akt. Honokiol also inhibited NF-κB-dependent reporter gene expression induced by TNFR1, TRADD, TRAF, NIK, and IκBβ (88). Consistent with honokiol’s effect on NF-κB, honokiol decreased levels of NF-κB target genes, including IAP1, IAP2, Bcl-xL, Bcl-2, cFLIP, TRAF1, and survivin (88). NF-κB and NF-κB-regulated gene expression inhibited by honokiol can thus enhance apoptosis. Honokiol also down-regulated NF-κB activation in an in vivo mouse dorsal skin model. Another study showed that honokiol blocked the production of TNF-α, MCP-1, interleukin-8, and ICAM-1 and was found to act at the level of IKK or upstream of IKK, indicating a possible mechanism of its anti-tumor action (89).

4. Summary

In recent years, various biologically active constituents have been isolated from TCM and have been found to have varied activity in experimental studies. Honokiol and magnolol have been found to have anti-oxidative, anti-inflammatory, anti-tumor, and anti-microbial properties in preclinical models. Their safety during long-term administration, combined with their cost and future therapeutic potential, makes them ideal therapeutic agents (90). In addition, magnolol and honokiol are small molecular weight natural products that are orally bioavailable and able to cross the blood-brain barrier. Clinical trials are needed to fully realize...
the potential of honokiol and magnolol as effective antitumor drugs. Honokiol and magnolol analogues with improved pharmacokinetic and pharmacodynamic properties will also encourage further advances.

Many studies have shown that both magnolol and honokiol induce apoptosis of many types of cancer cells, though those studies describe different mechanisms of action. Moreover, investigation of how they specifically induce apoptosis in cancers and spare normal cells will provide new clues to help identify more efficient drugs and to develop apoptosis-targeting therapies.

References

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