A Pharmacological Emphasized Revision on Alpha-Hederin

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Abstract
Herbal medicines are a great deal of attention to investigate emphasizing on health benefits. Alpha-hederin (α-HN) is a plant-derived saponin having a number of important biological activities. However, the studies on this component are not enough. This revision aims at summarizing the biological roles of α-HN including possible mechanism of actions. This study is made on the basis of evidence observed in electronic databases, Pumbed, Science Direct, Scopus, Web of Science and miscellaneous. A number of pharmacological actions of α-HN have been investigated, including antioxidant, anti-inflammatory, antiarthritic, bronchiolytic, antifungal, and antiparasitic activities. It also has anti-histaminic and antitumor activities. In addition, desmutagenic and hepatoprotective potentials also have been shown. Physiological zinc depletion and calcium influx are the two observed toxic events in α-HN treated rodents. However, it has synergistic effects with other chemicals, while antagonistic to a number of toxicants. The α-HN may be an interesting phytochemical, therefore, more researches are necessary for it.

Keywords: Alpha-hederin; Antioxidant; Anti-inflammatory; Anti-cancer; Hepatoprotective

Introduction
Hederagenin is the aglycone part of a numerous saponins found in Hedera helix (common ivy). It was discovered by L. Posselt in 1849 and named as the hederic acid [1]. The most prevalent of these being hederacoside C and alpha-hederin (α-HN) (Figure 1). The α-HN also to be found in Chenopodium quinoa, Kalopanax pictus and Nigella sativa plants. The α-HN, a monodesmosidic triterpenoid saponin having important biological activities [2,3]. It is white to off-white crystalline powder and also known as \(\text{[3β,4α]-3-[[2-O-(6-Deoxy-α-L-mannopyranosyl)-α-L-arabinopyranosyl]oxy]-23-hydroxyolean-12-en-28-oic acid}\). Its chemical formula is \(\text{C}_{41}\text{H}_{66}\text{O}_{12}\); molecular weight: 750.96 and melting point: 128-268ᴼC. The α-HN is stable under normal condition and incompatible with acids, reducing agents and oxidizing agents; soluble in ethanol, di-methyl sulfoxide and di-methylformamide.

The α-HN and its few analogues have been proven to have antioxidant, anti-inflammatory, cytotoxic and antitumor activities. The aim of this revision is forwarded to sketch the findings on α-HN in association with the possible mechanisms of action emphasizing on observed pharmacological activities. For this purpose, I have selected published articles in different databases such as ScienceDirect, PubMed, Web of Science, Scopus and miscellaneous. Then the articles were sorted according to the observed biological properties. Articles containing the same information with same compounds were replaced by the most recent one. However, other hederins are also considered in this study.

Search Strategy
"cytotoxicity", "genotoxicity" and "mutagenicity". No language restrictions were imposed. The search yielded 149 references. Then the list was reduced to 98 references, which were further scrutinized by reading each abstract and after discarding 60, attention was given on 38 papers.

**Findings on Alpha-hederin (α-HN)**

**In oxidation**

Mice when treated subcutaneously (s.c.) with 10 and 30mM/kg of α-HN for 3 days exhibited an increase in hepatic reduced glutathione (GSH), glutathione peroxidase (GPs) and glutathione-S-transferase (GST) levels. Although, there was a decreased in catalase (CAT) level with the highest treated dose (30mM/kg) but increased metallothionein (MT) with an elevation of hepatic Zn and Cu concentrations along with ascorbic acid concentration were demonstrated [4]. Otherwise, α-HN is evident to exhibit 1,1-di-phenyl-2-picryl-hydrazyl (DPPH), superoxide anion (O₂⁻•) and hydroxyl (•OH) radicals scavenging along with a significant lipid peroxidation (LP) potential [5].

Glutathione (GSH) is an important antioxidant in living systems, preventing damage to important cellular components caused by reactive oxygen species (ROS) such as free radicals, peroxides, lipid peroxides and heavy metals [6]. Otherwise, MTs, a cysteine-rich family with low molecular weight (MW: 500 to 14000 Da) proteins are localized to the membrane of the Golgi apparatus capable to bind with physiological and xenobiotic heavy metals (e.g.-Zn, Cu, Se, Cd, Hg) through its thiol group in cysteine residues. MTs are evident to provide protection against metal toxicity, mainly through the regulation of Zn and Cu and provide protection against oxidative stress [7]. Thus, along with the anti-radical power an increase in GSH and MT levels with the α-HN treatment confirming its potential antioxidant capacity.

**In inflammation and arthritis**

Ovalalum (OVA)-sensitized male adult guinea pigs (n=8) treated with 0.3-3.0mg/kg α-HN intraperitoneally (i.p.) significantly decreased the pro-inflammatory mediators interleukin (IL) -2,-4 and -17 with an increased level in interferon-gamma (IFN-γ) [8]. It also caused a decrease in histamine levels and white blood cells (WBCs), basophil and eosinophil counts with an increased in the neutrophil, lymphocyte and monocyte counts [9]. However, rats (n=6) treated with 0.02mg/kg (i.p.) caused a reduction in IL-2 and -17 mRNA levels with an increased in anti-arthritic and bronchiolytic effects through miRNA-133a gene expression [10]. Otherwise, α-HN also exhibited an anti-inflammatory activity in carrageenan and isoprenaline-induced animal models [2,11]. In the latter case it was supposed to act through inhibiting heterologous desensitization induced by high concentrations of muscarinic ligands like methacholine [11]. In addition, α-HN at 0.02 and 20mg/kg (i.p.) in carrageenan-induced acute edema rats imparted an anti-inflammatory effect by blocking Bradykinin and inflammation mediators [12].

To be mentioned that IL-2 and -4 are responsible for the proliferation of responsive T and B cells, respectively. In addition, IL-2 also acts on some B cells and causes stimulation to the growth factor and antibody production [13]. Otherwise, IL-17 is a potent pro-inflammatory cytokine produced by activated memory T cells [14]. However, the majority of ILs is synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. The IFN-γ (type II interferon) induces innate and adaptive immunity against viral, some bacterial and protozoal infections. It is an important activator of macrophages [15]. Thus, the increased levels of IL-2,-4,-17, IFN-γ and lymphocytes with the α-HN treatment may be due to its potential anti-inflammatory activity.

Otherwise, histamine, the organic nitrogenous compound produced by basophils and by mast cells found in nearby connective tissues, as a part of an immune response increases the permeability of the capillaries to WBC and some proteins, to allow them to engage pathogens in the infected tissues [16]. It involves in the inflammatory responses and has a central role as a mediator of pruritus [17]. In addition, neutrophil forms an essential part of the innate immune system [18]. However, along with innate immunity, monocytes take a part in the adaptive immunity. Arthritis, on the other hand, is a form of joint disorder involving inflammation in one or more joints, where pain comes from the inflammation. Otherwise, bronchitis is the inflammation of the bronchi in the lungs, including the symptoms of mucus, wheezing, shortness of breath, and chest discomfort. In addition, methacholine, a synthetic choline ester that acts as a non-selective muscarinic receptor agonist in the parasympathetic nervous system, which is primarily used to diagnose bronchial hyperreactivity and one of the hallmarks of asthma also occurs in chronic obstructive pulmonary disease [19]. The overall findings suggesting to consider the α-HN as a hopeful anti-inflammatory, anti-arthritic and bronchiolytic agent.

**Against fungi and parasites**

α-HN was found to act against Candida albicans with 6.25, 12.5 and 25µg/mL. Along with the modification of cellular contents and alterations in the cell envelope, it caused degradation and death of C. albicans with a half minimal inhibitory concentration (IC₅₀) of 25µg/mL [20]. The α-HN also exhibited anti-Leishmania promastigotes activity with or without treatment with β-hederin (β-HN) (Figure 1). A cytotoxic activity against human monocytes (THP1 cells) was also observed alongside this treatment. However, in both cases α-HN (IC₅₀: 0.25 to 13.6µM) was founded more potent than β-HN (IC₅₀: 2.25 to 3.17µM), as it leaded a strong anti-proliferative activity on all stages of development of the parasite with an alteration in the membrane integrity and potential [21,22].

C. albicans, a diploid fungus presents oral and genital infections and candidal onychomycosis in human. However, systemic fungal infections may lead to morbidity and mortality in
immunocompromised patients (e.g. -AIDS, cancer chemotherapy, organ or bone marrow transplantation) [23,24]. Otherwise, Leishmaniasis, in human is caused by more than 20 species of Leishmania. It presents ulcer of the skin, mouth, and nose with fever, low red blood cells (RBCs), and enlarged spleen and liver [25,26].

In cancer

![Figure 1: Chemical structures of hederacosides and respective derived hederins.](image)

Both α-HN and delta-hederin (δ-HN) (Figure 1) are evident to cause membrane pore formation. Their introduction inside the cell is assumed via sterol-dependent pathway [27,28]. An earlier report also suggesting α-HN to cause vacuolization of the cytoplasm and alteration of the cell membrane leading to cell death in melanoma and non-cancer mouse 3T3 fibroblasts cells [29]. Otherwise, an upregulation of nuclear factor kappa B (NF-κB) and Caspase-3 dependent pathways leading to produce nitric oxide (NO) and ROS are evident to cause oxidative damage of cells in BALB/C mice and murine leukemia P388 cells, respectively [30,31]. In MCF-7 and MDA-MB-231 human breast cancer cells, α-HN (0.008-10µg/mL) induced apoptosis and caused a depolarization of mitochondrial membrane potential leading to release of Apaf-1 (apoptosome) and cytochrome c and activation of Caspase-3 and -9 [3]. The α-HN (8-20µM) is also evident to induce cell necrosis and apoptosis in HEp-2 (larynx carcinoma) cells [32]. However, α-HN (0.1-5µM) with pentoxifylline exhibited cytotoxicity by downregulation of the mRNA levels of TNF-α and IL-6 in murine hepatoma (HePa-1c1c7) and murine macrophage (RAW 264.7) cell lines [33].

On the other hand, β-HN, other than α-HN exhibited significant cytotoxic activity in human HeLa, MCF-7, HL-60, HT1080 and HepG2 cell lines, where the IC50 values were found in between 4.74 and >100µM [34]. However, α-HN also found to act against a number of human cancer cell lines including colon cancer (HT-29) with 5-fluorouracil (5-FU) and 3-O-alpha-L:-rhamnopyranosyl-(1→2)-alpha-L:-arabinopyranoside [35,36]. In both cases, the activity was considered synergistic as the co-treated groups caused significant death of the tested cell lines than the individually treated groups. In addition, α-HN also evident to produce an antitumor activity against murine leukemia (P388) and Lewis lung carcinoma (LL/2), human kidney (HEK293), smooth muscle (HASM) and tranfection of HEK293 cell lines [37,38]. Otherwise, α-HN and/or its α-HN chitosan nanoparticles (α-HN-CS-CD147-NPs) (148.23 ±1.75nm) at a dose of 50µg/mL exhibited strong antitumor activity on HepG2 and SMMC-7721 cell lines. However, the activity of α-HN-CS-CD147-NPs was considered more prominent than α-HN [39].

To be mentioned that the α-HN (0.13-13nM/mL) was found non-mutagenic in doxorubicin (DOX)-induced toxicity in human lymphocytes [40].

The NF-κB can be stimulated by stress, cytokines, free radicals and so on [41]. The activated NF-κB is translocated into the nucleus after binding to specific sequences of DNA (response elements) and recruits other proteins such as co-activators.
and RNA polymerase, leading to transcribe downstream DNA into mRNA, which results in a change of cell function [42]. Thus an incorrect regulation of NF-kB may be linked to cancer, inflammatory and autoimmune diseases, immune-suppression and other diseases [43]. The source of ROS is a vast. ROS, the chemically reactive molecules containing oxygen like peroxides, $O_2•-\bullet$ OH, and singlet oxygen have an important role in cell signaling and homeostasis [44]. However, excess production of ROS is involved in cellular detrimental effects, including cell death and cancer. Otherwise, NO is also an important cellular signaling molecule and a powerful vasodilator with a short half-life [45]. NO can be produced by NOS dependent and independent pathways. Along with a number of beneficial effects, excess amount of NO can contribute to repercussion injury following a period of ischemia and by reacting with superoxide ($O_2•-\bullet$), it produces the damaging oxidant peroxynitrite. The α-HN in BALB/c mice and murine leukemia P388 cells [30,31] produced cytotoxicity via over production of ROS and NO may be the detrimental effects of it. However, in MCF-7 and MDA-MB-231 human breast cancer cells α-HN induced apoptosis and depolarization of mitochondrial membrane potential [3] and in Hep-2 (larynx carcinoma) cells necrosis and apoptosis [32] may be linked to the α-HN-mediated pro-oxidant activity as the upregulation of NF-kB may link to oxidative stress. In addition, Caspase-9, the initiator Caspase encoded by the CASP9 gene is linked to the mitochondrial death pathway. It is activated during programmed cell death (apoptosis). After an induction of stress signaling pathways Jun amino terminal kinase (JNK)/Stress-activated protein kinases (SAPK) causes the release of cytochrome c from the mitochondria and activation of Apaf-1. On the other hand, Caspase-3 (encoded by CASP3 gene) is a Caspase protein that interacts with Caspase-8 and Caspase-9, sequential activation of which results in cell apoptosis. Thus the activation of Caspase-3 and -9 and release of Apaf-1 and cytochrome c is linked together during programmed cell death. Otherwise, the IL-6 (encoded by IL6 gene) may act as both a pro-inflammatory cytokine and an anti-inflammatory myokine [46]. IL-6 is secreted by T cells and macrophages to stimulate immune response, eg. during infection and after trauma, especially burns or other tissue damage leading to inflammation. Otherwise, during signaling pathways of TNF-α, NF-kB, translocates to the nucleus and mediates the transcription of a vast array of proteins involving in cell survival and proliferation, inflammatory response, and anti-apoptotic factors. Thus, the downregulation of IL-6 and TNF-α in the murine hepatoma (Hepa-1c1c7) and murine macrophage (RAW 264.7) cell lines [33] is helpful for cell death.

On hepatic system

Liu et al. [47] suggested that α-HN is hepatoprotective through the suppression of P450 system in acetaminophen-, bromobenzene-, carbon tetrachloride (CCL4)-, furosemide-, thioacetamide-, chloroform (CHCl3) and dimethylnitrosamine-induced liver injury in mice. Shi & Liu [48] also found a similar activity when mice were treated with α-HN and/or sapindoside B (Figure 1) at 20mg/kg (s.c.) for 3 days. Jeong [49] suggested α-HN specifically decrease the activities of cytochrome P (CYP)-4501A1, -4501A2, and -4502E1. There was also a demonstration about the downregulation of the activities of microsomal ethoxyresorufin O-deethylase, methoxyresorufin O-demethylase and aniline hydroxylase. However, the animals of the co-treatment group were significantly protected than the groups treated with α-HN and sapindoside alone. Before this, Liu et al. [50] found an increased levels of hepatic MTT-1 and -II in cadmium (Cd)-induced liver injured mice with the s.c. treatment of α-HN at 10-300mM/kg. Otherwise, prevention in the augmented levels of serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and LP activities was also noted in CCl4-induced hepatotoxic mice [51]. In addition, α-HN (0.1-20µM) is also evident to cause suppression of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced Cypla-1 gene expression with an antagonistic effect of the DNA binding potential of a nuclear Ah receptor in mouse hepatoma (Hepa-1c1c7) cell line [52].

CYP4501A1 is a substrate-inducible microsomal enzyme that oxygenates polycyclic aromatic hydrocarbons, especially those are carcinogenic to convert them as water-soluble derivatives [53]. Diseases associated with CYP4501A1 include ehrlich tumor carcinoma and pyridoxine deficiency. Otherwise, CYP4501A2 is a monoxygenase protein, catalyzes many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. However, it is able to metabolize some polycyclic aromatic hydrocarbons (PAHs) to carcinogenic intermediates. Other xenobiotic substrates for this enzyme include caffeine, aflatoxin B1, and acetonaphen. It metabolizes arachidonic acid to 19-hydroxyeicosatetraenoic acid (19-HETE), which constricts arterioles, elevates blood pressure, promotes inflammation responses, and stimulates the growth of various types of tumor cells [54]. CYP4502E1 gene, especially encodes a member of the cytochrome P450 super-family of enzymes. Ethoxyresorufin [55], methoxyresorufin and aniline appear to be metabolized by a group of CYP450 isoenzymes. Thus, the decreased levels of CYP450 enzymes-mediated low microsomal ethoxyresorufin O-deethylase, methoxyresorufin O-demethylase and aniline hydroxylase levels [49] may be linked in. MT protein acts as a primary metal storage, transport and detoxification [56]. In addition, ALT, LDH and LP are the biomarkers considered during liver injury. Thus, the modulatory effects on the overall genes and other biomarkers may be associated in hepatoprotective potential of α-HN.

Miscellaneous

Rats when treated with α-HN exhibited Zn depilation with a decreased fetal weight and increased the incidence of abnormal fetuses at high dose (300mM/kg) [57]. Duffy et al. [58] suggested a secondary Zn deficiency in rats treated with α-HN at 20 or 30mM/kg for 10 days. Male Wistar rat isolated stomach corpus and fundus strips treated with α-HN (100µM) exhibited Ca2+ influx via voltage-dependent calcium channels of L-type [59].
Zinc (Zn\(^{2+}\)) is found in nearly 100-300 specific enzymes, serving as a structural ion in transcription factors and is stored and transferred in MPs [60]. Zn is a key factor in prostate gland function and reproductive organ growth [61], metabolism of RNA and DNA, signal transduction as well as gene expression. It also regulates apoptosis and modulates brain excitability [62]. However, the augmented level of Zn can be toxic to the nervous system [63]. On the other hand, intracellular calcium (Ca\(^{2+}\)) may cause oxidative stress and apoptosis to the cells, and thus producing several diseases, especially cardiac myocyte experiences with Ca\(^{2+}\) influx. It also impairs kidney function and decreases absorption of other minerals [64,65]. Thus, Zn\(^{2+}\) depilation and Ca\(^{2+}\) influx phenomena may be a major concern to the toxicological studies of α-HN [66]. The overall findings in a brief are shown in Table 1.

Table 1: Findings on α-hederin (along with other chemical moieties) in a brief.

<table>
<thead>
<tr>
<th>Dose(drug)/Route of Administration</th>
<th>Test System</th>
<th>Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 and 30mM/kg (s.c.) for 3 days</td>
<td>In mice</td>
<td>Increased liver GSH, GPx and GST levels. Decreased CAT with 30mM/kg but increased MP with an elevation of hepatic Zn and Ca concentrations along with ascorbic acid concentration</td>
<td>Liu &amp; Liu [4]</td>
</tr>
<tr>
<td>-</td>
<td>Antioxidant tests: DPPH, O(_2)(\cdot), H(_2)O(_2) free radical scavenging, total antioxidant activity, reducing power and metal chelating activities</td>
<td>Anti-radical, at concentration of 75pg/mL showed 94% inhibition on LP</td>
<td>Gülçin et al. [5]</td>
</tr>
<tr>
<td>0.3-3.0mg/kg (i.p.)</td>
<td>In OVA-sensitized male adult guinea pigs (n=8)</td>
<td>Decreased levels of IL-2, IL-4 and IL-17 with an increased level of IFN-γ</td>
<td>Keyhanmanesh et al. [8]</td>
</tr>
<tr>
<td>0.3-3.0mg/kg (i.p.)</td>
<td>In OVA-sensitized male adult guinea pigs (n=8)</td>
<td>Decreased histamine levels and WBC, basophil and eosinophil counts; increased in neutrophil, lymphocyte and monocyte counts</td>
<td>Saadat et al. [9]</td>
</tr>
<tr>
<td>0.02mg/kg (i.p.)</td>
<td>OVA-sensitized male rats (n=6)</td>
<td>Decreased IL-2 and IL-17 mRNA levels with an increased in miRNA-133 a gene expression</td>
<td>Ebrahimi et al. [10]</td>
</tr>
<tr>
<td>With its methyl ester at 60mg/kg (p.o.)</td>
<td>In carrageenan-induced edema rats and mice</td>
<td>Produced anti-arthritis activity</td>
<td>Li et al. [2]</td>
</tr>
<tr>
<td>0.02 and 20mg/kg (i.p.)</td>
<td>In carrageenan-induced acute paw edema in rats (n=7)</td>
<td>Imparted anti-inflammatory effects by blocking bradykinin or other inflammation mediators</td>
<td>Gepdiremen et al. [12]</td>
</tr>
<tr>
<td>1 and 100µM</td>
<td>On isoprenaline-induced relaxation in bovine tracheal smooth muscle strips.</td>
<td>Bronchioletic effect by inhibiting heterologous desensitization induced by high concentrations of muscarinic ligands like methacholine</td>
<td>Wolf et al. [11]</td>
</tr>
<tr>
<td>100µM</td>
<td>On male wistar rat isolated stomach corpus and fundus strips</td>
<td>Cholinergic pathways do not participate in α-HN-evoked contraction</td>
<td>Mendelet al. [58]</td>
</tr>
<tr>
<td>6.25, 12.5 and 25µg/mL</td>
<td>On Candida albicans</td>
<td>Induced modification of cellular contents and alterations of cell envelope with degradation and death with an IC50 of 25μg/mL</td>
<td>Moulin-Traffort et al. [20]</td>
</tr>
<tr>
<td>With β-HN</td>
<td>In Leishmania promastigotes and human monocytes (THP1 cells).</td>
<td>Exhibited strong anti-proliferative activity on all stages of development of the parasite by altering membrane integrity and potential. α-hederin produced IC50 = 0.25 to 13.6μM, while β-hederin by 2.25 to 3.17μM</td>
<td>Delmas et al. [21]</td>
</tr>
<tr>
<td>With β-HN</td>
<td>On Leishmania Mexicana in their promastigote and amastigote forms</td>
<td>Exhibited strong anti-proliferative activity on all stages of development of the parasite</td>
<td>Ridoux et al. [22]</td>
</tr>
<tr>
<td>-</td>
<td>On mouse B16 melanoma and non-cancer mouse 3T3 fibroblasts cells</td>
<td>Induced vacuolization of the cytoplasm and membrane alterations leading to cell death</td>
<td>Danky et al. [29]</td>
</tr>
<tr>
<td>0.5 and 1µM</td>
<td>In BALB/C mice</td>
<td>Stimulated NO release via upregulation of iNOS expression through NF-kB transactivation.</td>
<td>Jeong &amp; Choi [30]</td>
</tr>
<tr>
<td>Concentration</td>
<td>Effect</td>
<td>Cells</td>
<td>Notes</td>
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<tr>
<td>0.008-10µg/mL</td>
<td>Caused disruption of mitochondrial membrane potential and subsequently increased the production of ROS with Caspase-3 activation</td>
<td>In murine leukemia P388 cells</td>
<td>Swamy &amp; Huat [31]</td>
</tr>
<tr>
<td>0.008-10µg/mL</td>
<td>Induced apoptosis and caused a depolarisation of mitochondrial membrane potential leading to release of Apaf-1 and cytochrome c and activation of Caspase-3</td>
<td>In MCF-7 and MDA-MB-231 human breast cancer cells</td>
<td>Cheng et al. [3]</td>
</tr>
<tr>
<td>With CP and TQ at 6-14µM</td>
<td>Enhanced neither cytotoxicity nor apoptosis of these cancer cells (IC50 values ranging from 5.4-27.1µM)</td>
<td>On human A549 (lung carcinoma), Hep-2 (larynx epidermoid carcinoma), HT-29 (colon adenocarcinoma) and Mia PaCa-2 (pancreas carcinoma) cell lines</td>
<td>Rooney &amp; Ryan [32]</td>
</tr>
<tr>
<td>8-20µM</td>
<td>Produced necrosis and apoptosis activity</td>
<td>In HEp-2 (larynx carcinoma) cells</td>
<td>Rooney &amp; Ryan [32]</td>
</tr>
<tr>
<td>With pentoxifylline at 0.1- 5µM</td>
<td>Decreased production of production and mRNA levels of TNF-α and IL-6</td>
<td>In murine hepatoma (Hepa-1c1c7) and murine macrophage (RAW 264.7) cell lines</td>
<td>Kim et al. [33]</td>
</tr>
<tr>
<td>β-HN</td>
<td>Cytotoxic activity with the IC50 values between 4.74 to &gt;100µM</td>
<td>On HeLa, MCF-7, HL-60, HT1080 and HepG2 cell lines</td>
<td>Liu et al. [34]</td>
</tr>
<tr>
<td>With δ-HN</td>
<td>Pore formation and sterol-dependent introduction into the cells</td>
<td></td>
<td>Lorent et al. [27]</td>
</tr>
<tr>
<td>With 3-O-alpha-L- rhamnopyranosyl-(1--&gt;2)-alpha-L- arabinopyranoside</td>
<td>Significant anticancer activity</td>
<td>In human cancer cell lines (A-549, SK-OV-3, and SK-MBL-2)</td>
<td>Bang et al. [35]</td>
</tr>
<tr>
<td>With 5-FU at 0.001-100µM</td>
<td>Synergistic anticancer effects</td>
<td>On colon adenocarcinoma (HT-29) cell line</td>
<td>Bun et al. [36]</td>
</tr>
<tr>
<td>5 and 10mg/kg mg/kg (p.o.) for 7 days</td>
<td>Antitumor activity</td>
<td>In murine leukemia (P388) and Lewis lung carcinoma (LL/2) cell lines in C57BL/6 x DBA/2 mice</td>
<td>Kumara &amp; Huat [37]</td>
</tr>
<tr>
<td>1µM</td>
<td>Antitumor activity against the cell lines</td>
<td>On human kidney cells (HEK293), smooth muscle cells (HASM) and tranfection of HEK293 Cells</td>
<td>Sieben et al. [38]</td>
</tr>
<tr>
<td>With α-HN chitosan nanoparticles (148.23 ± 1.75nm) 50µg/mL</td>
<td>Strong antitumor activity of α-HN-CS-CD147-NPs</td>
<td>In HepG2 and SMMC-7721 cell lines</td>
<td>Zhu et al. [39]</td>
</tr>
<tr>
<td>0.13-13nM/mL</td>
<td>Produced a desmutagenic effect</td>
<td>In DOX-induced toxicity in human lymphocytes</td>
<td>Amara-Mokrane et al. [40]</td>
</tr>
<tr>
<td>10-300mM/kg (s.c.)</td>
<td>Increased hepatic MP-1 and -II levels. Exhibited hepato protectivity</td>
<td>In Cd-induced liver injury mice</td>
<td>Liu et al. [49]</td>
</tr>
<tr>
<td>30mM/kg (s.c.) for 3 days</td>
<td>Exhibited hepatoprotective activity with a suppression of P450</td>
<td>In acetaminophen-, bromobenzene-, CCl4-, furosemide-, thioacetamide-, CHCl3 and dimethylnitrosamine-induced liver injury in mice</td>
<td>Liu et al. [46]</td>
</tr>
<tr>
<td>With sapindoside B at 20mg/kg (s.c.) for 3 days</td>
<td>Hepatoprotective activity with a suppressive effect on liver cytochrome P-450</td>
<td>In mice (n=5)</td>
<td>Shi &amp; Liu [47]</td>
</tr>
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<td>-</td>
<td>Significantly decreased the hepatic content of P450 and the activities of microsomal ethoxyresorufin O-deethylase, methoxyresorufin O-demethylase, and aniline hydroxylase, representative activities of CYP-4501A1, -4501A2, and -4502E1 other than P4502B</td>
<td></td>
<td>Jeong [48]</td>
</tr>
<tr>
<td>-</td>
<td>Significantly prevented the increase in serum ALT, LDH and LP activities in a dose dependent manner</td>
<td>On CCl4-induced hepato toxic mice</td>
<td>Jeong &amp; Park [50]</td>
</tr>
</tbody>
</table>
Conclusion

Revision accounts α-HN to have antioxidant, anti-inflammatory, antiarthritic and bronchiolytic effects. Along with antifungal and antiparasitic activities α-HN is also a potent cytotoxic agent. Antitumor activity is also demonstrated against a number of cancer cell lines. In addition, α-HN has desmutagenic hepatoprotective potential.

Featuring

The methyl ester of α-HN (60mg/kg, p.o.) is evident to produce strong anti-arthritis activity in carrageenan-induced edema rats and mice [2]. Otherwise, with cisplatin (CP) and thymoquinone (TQ), α-HN at 6-14µM exhibited neither cytotoxicity nor apoptosis on the human A549 (lung carcinoma), Hep-2 (larynx epidermoid carcinoma), HT-29 (colon adenocarcinoma) and Mia PaCa-2 (pancreas carcinoma) cell lines [32]. Although, physiological Zn²⁺ depletion and Ca²⁺ influx in experimental animals are reported, but synergistic effects with other chemicals as well as antagonistic effects of number of toxicants making α-HN as an interesting chemical in the advances in pharmacological studies.

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Conflict of Interest

I have no conflict of interest.

References


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