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REVIEW ARTICLE

ARCTIGENIN, A PLANT LIGNAN WITH TREMENDOUS POTENTIAL: A REVIEW

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ABSTRACT

Arctigenin is a phenylpropanoid dibenzylbutyrolactone lignan which can be obtained from plants. It has shown tremendous potential in neurological diseases and cancers. The literature furnishes numerous data on their anti-inflammatory, antioxidant, antiproliferative, hepatoprotective, antitumor, antimicrobial, antifungal, immunomodulatory, anti-aging and hypoglycemic activities. It has been found potent in vitro anti-influenza A virus and neuroprotective against Japanese encephalitis in a mouse model. It has been also reported useful in Alzheimer disease. The aim of this study was to overview the therapeutic effects of arctigenin. Our study suggests that different medicinal properties of Arctigenin require more studies regarding to other unknown useful features of this valuable plant lignan.

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INTRODUCTION

The importance of herbs to cure of human ailment cannot be ignored. Since ancient time plant products have been used as medicine. In indigenous system like Ayurved and Unani phytomedicines are used to heal several diseases. In last three decades inclination of people has been again shifted towards natural products due to side effects of Synthetic drugs. Hence plants are an important source of phytochemicals having medicinal value. One of such plant product is Arctigenin which is a lignan obtained from *Arctium lappa* (Asteraceae), *Bardane fructus* (Asteraceae), *Cincus benedictus*(Asteraceae), *Forsythia intermedia* (Oleaceae), *Merremia gemella* (Convolvulaceae), *Ipomoea cairica* (Convolvulaceae), *Saussurea medusa* (Asteraceae) and *Torreya nucifera* (Taxaceae) (Srivastava, 2016). Chemically it is a phenylpropanoid dibenzylbutyrolactone lignan (Fig. 1). Arctigenin has been reported having great potential against various human disorders. This review focuses on the reported medicinal properties of this compound obtained from different plants so that it would be easy to assess the potential of this compound.

Anti-allergic effect

The anti-allergic effects of Arctigenin using immunoglobulin E (IgE)-activated RBL-2H3 cells were evaluated. The results suggest that arctigenin plays an important role in the anti-allergic effects; it inhibited the activation of the FcεRI receptor induced by the antigen-IgE complex. Arctigenin significantly inhibit U266 cells of IgE production in dose dependent manner without any sign of cytotoxicity. Arctigenin also non-toxically abolished IL-4 and anti-CD40 stimulated IgE production by PBMCs from food allergic patients. Arctigenin inhibited IgE production in human B cell line and food allergic patient PBMCs. Arctigenin blocked anaphylactic reactions in a murine model of peanut allergy. Hence, Arctigenin have potential for treatment of IgE associated inflammatory diseases (Liu *et al*., 2016).

Anti-diabetes activity

Arctigenin, increases AMPK (AMP-activated protein kinase) phosphorylation and stimulates glucose uptake in cultured L6 skeletal muscle cells and isolated muscles, while inhibiting gluconeogenesis and lipid synthesis in primary hepatocytes. AMPK has been identified as striking target for the development of innovative molecules to treat type-2 diabetes. Arctigenin also inhibits the respiration of L6 myotubes and of isolated mitochondria through a specific effect on respiratory complex I. Constant administration of arctigenin lowers blood glucose levels and improves lipid metabolism in ob/ob mice, while acute oral administration is effective in inhibiting gluconeogenesis even in wild-type mice. Based on this evidence, it was concluded that arctigenin activates AMPK by

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inhibiting respiratory complex I and improves metabolic derangement in the ob/ob mouse model (Huang *et al*., 2011).

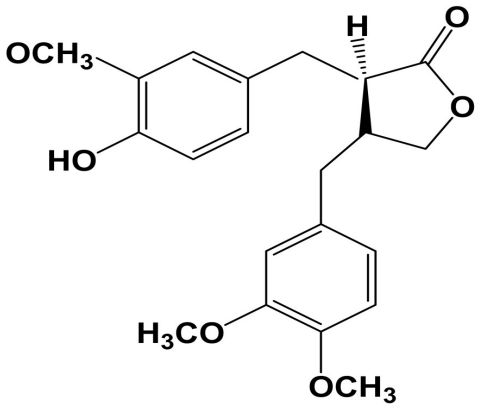

Fig.1. Chemical structure of Arctigenin

Antiulcer activity

The antiulcer activity of arctigenin against ulcers induced by absolute ethanol and acetic acid was evaluated in a Sprague-Dawley rat model. In the ethanol-induced model, arctigenin inhibited gastric lesions in a dose-dependent manner. It also reduced MDA and increased superoxide dismutase levels in serum when compared with the vehicle group. In addition, the expression levels of tumor necrosis factor-α, interleukin-6 (IL-6), IL-10 and C-reactive protein were significantly decreased in the arctigenin treated group compared with the vehicle group. Thus, this study indicated that arctigenin exerted antiulcer activity, which may be associated with its reduction in oxidative and inflammatory damage (Li *et al*., 2016).

Antioxidant activity

Studies on L6 cells and skeletal muscles of the rats showed that arctigenin effectively increased the expression of the antioxidant-related genes, including superoxide dismutase (SOD), glutathione reductase (Gsr), glutathione peroxidase (GPX1), thioredoxin (Txn) and uncoupling protein-2(UCP2), by regulation of two potential antioxidant pathways: AMPK/PGC-1α/PPARα in mitochondria and AMPK/p53/Nrf 2 in the cell nucleus. It efficiently enhances rat swimming endurance by increasing the antioxidant capacity of the skeletal muscles, Hence arctigenin, has potential to be used as an antioxidant in the treatment of fatigue and related diseases (Wu *et al*., 2014)

Hepatoprotective effect

In a study, two hepatocellular carcinoma (HCC) cell lines (Hep G2 and SMMC7721) were used to investigate the antihepatoma potential of arctigenin and the molecular mechanisms involved in this process. It was found that arctigenin-induced apoptotic effect on Hep G2 was stronger than that on SMMC7721 because arctigenin exert different effects on apoptosis-related factors, e.g., PI3K/p-Akt, NF-κB and p53, in Hep G2 and SMMC7721(Lu *et al*., 2015).

Anti-obesity activity

Studies on anti-obesity activities of arctigenin showed that it reduce weight gain, fat pad weight, and triglycerides in HFD-induced obese mice. Arctigenin inhibit the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα) in vitro and in vivo. It also induces the AMPK activation resulting in down-modulation of adipogenesis-related factors including PPARγ, C/EBPα, fatty acid synthase, adipocyte fatty acid-binding protein, and lipoprotein lipase. The study demonstrates that Arctigenin can reduce key adipogenic factors by activating the AMPK in vitro and in vivo and suggests a therapeutic implication of Arctigenin for obesity treatment (Han *et al*., 2016).

Anti-inflammatory

Arctigenin anti-inflammatory activity was evaluated in the animal models including myeloperoxidase (MPO) and eosinophil peroxidase (EPO) activities in the edematous tissues homogenate, and silica-induced reactive oxygen species (ROS) production in the RAW 264.7 cell line. It was found that arctigenin significantly decreased not only carrageenan-induced paw edema after injection of carrageenan, arachidonic acid (AA), but also MPO and EPO activities in the AA-induced edematous tissues homogenate as indicators of neutrophils and eosinophils recruitment into the inflamed tissue. It was suggested that the mechanism of action of arctigenin may be due to the inhibition or release in production of inflammatory mediators such as AA metabolites and free radicals. Hence, Arctigenin have significant anti-inflammatory action by inhibition of the exudation, and leukocytes recruitment into the inflamed tissues (Kang *et al*., 2008).

Inhibition of Nitric Oxide production

Zhao *et al*., 2009 evaluated the inhibitory effect of arctigenin on the overproduction of nitric oxide (NO) and determined the level of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). The inhibitory effect on the enzymatic activity of cyclooxygenase-2 (COX-2) and expression of inducible nitric oxide synthase (iNOS) was also tested. Arctigenin suppressed lipopolysaccharide (LPS)-stimulated NO production and pro-inflammatory cytokines secretion, including TNF-α and IL-6 in a dose-dependent manner. Arctigenin also strongly inhibited the expression of iNOS and iNOS enzymatic activity, whereas the expression of COX-2 and COX-2 enzymatic activity were not affected by arctigenin (Yao *et al*., 2012).

In Parkinson's disease

The neuroprotective effects of arctigenin on 1methyl-4 phenylpyridium ion and 1methyl 4 phenyl 1,2,3,6 tetrahydropyride induced neurotoxicity were examined and the results indicated that arctigenin could improve the movement behaviours and up-regulate dopamine and y-aminobutyric acid levels in a 1-methyl-4phenyl-1,2,3,6-tetrahydropyride induced neurotoxicity mouse model. The pretreatment with arctigenin on cultured human neuroblastoma SH-SY5Y cells could attenuate the decrease of cell survival rates caused by treatment with 1-methyl-4-phenylpyridinium ion by acting against cell apoptosis through the decrease of Bax/Bcl-2 and caspase-3 and by anti-oxidative action through reduction of the surplus reactive oxygen species production and down-regulation of mitochondrial membrane potential. Due to this effect arctigenin could be useful as a therapeutic agent for Parkinson's disease (Li *et al*., 2014).

Heat Shock response

Arctigenin inhibited the acquisition of thermo-tolerance in mammalian cells, including cancer cells. Arctigenin suppressed the response at the level of the activation of heat shock transcription factor, the induction of mRNA, and the synthesis and accumulation of Hsp. Thus, arctigenin seemed to be a new suppressive regulator of heat shock response in mammalian cells, and may be useful for hyperthermia cancer therapy (Ishihara *et al*., 2006).

Neuro-protective effect

Arctigenin treatment improved neurological function by reducing brain water content and hematoma and accelerating wound closure relative to untreated mice. Arctigenin treatment reduced the levels of TNF-α and IL-6 and the number of allograft inflammatory factor (IBA) and myeloperoxidase (MPO) positive cells and increased the levels of IL-10. Arctigenin treated mice had fewer apoptotic neurons and activated caspase-3-positive neurons surrounding the lesion than controls, indicating increased neuronal survival. Arctigenin treatment confers neuro-protection of brain tissue through anti-inflammatory and anti-apoptotic effects in a mouse model of SWI. These results suggest a new strategy for promoting neuronal survival and function after CED to improve long-term patient outcome (Song *et al*., 2016**;** Huang *et al* 2017).

Anti- colorectal cancer

Arctigenin induce cell cycle arrest and apoptosis in CT26 cells through the intrinsic apoptotic pathway via MAPKs signaling. In several metastatic phenotypes, Arctigenin controlled epithelial-mesenchymal transition (EMT) through increasing the expression of epithelial marker E-cadherin and decreasing the expressions of mesenchymal markers; N-cadherin, vimentin and catenin. Moreover, Arctigenin inhibited migration and invasion through reducing of matrix metalloproteinase-2 (MMP-2) and MMP-9 expressions. Arctigenin significantly inhibited lung metastasis of CT26 cells which demonstrates the inhibitory effects of Arctigenin on colorectal metastasis (Han *et al*., 2016).

Hepatoprotective effects

Human hepatocellular carcinoma (HCC) cells were treated with different concentrations of arctigenin and cell viability and apoptosis were assessed. Arctigenin significantly inhibited the viability of HCC cells in a concentration-dependent manner. Arctigenin induced apoptosis and activation of caspase-9 and 3. Over-expression of a constitutively active Akt mutant blocked arctigenin-induced apoptosis. Combinational treatment with arctigenin and the PI3-K inhibitor LY294002 significantly enhanced apoptosis. Arctigenin reduced the expression of Bcl-xL, Mcl-1, and survivin and the phosphorylation of mTOR and S6K, which were significantly reversed by over expression of constitutively active Akt. According to this report the anticancer activity of arctigenin in HCC cells, is mediated by inactivation of PI3-K/Akt signaling (Jiang *et al*., 2015).

Anti-aging effect

Aging is associated with structural deterioration of a number of cellular organs, including skin and muscle. Recently it has been known that miRNA-431 promotes muscle regeneration by suppressing the expression of SMAD4, suggesting that inhibition of SMAD4 may promote the regenerative capacity of aged muscles. Arctigenin, by increasing the expression of its target gene, it may decrease the expression of SMAD4. Thereby, it may promote myogenic capacity of human skeletal muscle cells**.** Hence, Arctigenin can be used to promote the regenerative capacity of aged muscles; and regenerate the lost muscles in traumatic injury (Correa *et al*., 2016).

Anti-ovarian cancer effect

Recently the effects of arctigenin on ovarian cancer cells were studied. Human ovarian cancer OVCAR3 and SKOV3 cells were treated with arctigenin, and cell proliferation and apoptosis were assessed. Arctigenin treated cells showed a 4-6 times increase in the percentage of apoptosis, compared with control cells. Arctigenin treatment significantly inhibited STAT3 phosphorylation and survivin and iNOS expression. Arctigenin-induced apoptosis was impaired by pre-transfection with survivin-expressing plasmid or addition of chemical nitric oxide (NO) donors. Additionally, exogenous NO prevented the suppression of STAT3 phosphorylation and survivin expression by arctigenin. Arctigenin treatment inhibits the proliferation and induces caspase-3-dependent apoptosis of ovarian cancer cells. Suppression of iNOS/NO/STAT3/ survivin signalling is causally linked to the anticancer activity of arctigenin. Therefore, arctigenin may be applicable to anticancer therapy for ovarian cancer (Huang *et al*., 2014).

Anti-Arrhythmic effect

The anti-arrhythmic effects of arctigenin *in vivo* and *in vitro* demonstrated that treatment with arctigenin could correct the aconitine-induced abnormal *I* Na, *I* Ca, L and *I* to by inhibiting the *I* Na and *I* Ca, L and enhancing the *I* too**.** Heart disease remains a major threat to human health. Ideal anti-arrhythmic drugs should focus on targeting both multiple and non-channel targets. Multi-channel effectors regulate ion channels to regain the integrative balance between the various channels and have a lower arrhythmoginic effect than the single channel blockers. This study provided both *in vivo* and electrophysiological evidences for the anti-arrhythmia effect of arctigenin; this compound mitigated the disturbances in ion channel function by affecting the currents and the activation/inactivation and action potential of rat myocardial cells. This study laid a foundation for the further investigation and application of the anti-arrhythmic effect displayed by arctigenin. (Zhao *et al*., 2013)

Anti-psoriasis effect

Keratin17 (K17), an ectopically expressed keratin in psoriatic lesions, plays a critical role in the pathogenesis of psoriasis. The optimized skin-penetrating gel form of arctigenin was applied on the imiquimod (IMQ)-induced psoriasis-like ear skin in mice. After treatment with arctigenin, IMQ-induced skin incrassation was effectively attenuated accompanying with the reduced weight of spleen. The afflicted skin tissues in the arctigenin-treated group displayed lower K17 expression level and higher AMP-activated protein kinase (AMPK) phosphorylation level compared with those in the model group. In vitro experiments further supported that arctigenin not only delayed keratinocyte proliferation arresting at G2/M cell cycle phase but also induced cell apoptosis. Therefore, arctigenin

may be used as a promising drug for psoriasis treatment (Du *et al*., 2016).

Anti-Arthritis effect

Rheumatoid arthritis fibroblast-like synoviocytes (RAFLSs) play an important role in the initiation and progression of Rheumatoid Arthritis, which are resistant to apoptosis and proliferate in an anchorage-independent manner. The effects of arctigenin on the proliferation and apoptosis of RAFLSs revealed that it inhibits cell proliferation and induces mitochondrial apoptosis of RAFLSs, which is associated with the modulation of NF-κB and Akt signaling pathways. Hence, it has potential anti-arthritis effect (Liu *et al*., 2015).

Antiviral activity against Influenza A virus

Arctigenin showed potent *in vitro* antiviral activities against influenza A virus (A/NWS/33, H1N1) (IFV). Based on the data from time-of-addition experiments and on release tests of progeny viruses, arctigenin was assumed to interfere with early event(s) of viral replication after viral penetration into cells, and to suppress the release of progeny viruses from the host cells. This work suggests that arctigenin can be useful in treatment for influenza (Hayashi *et al*., 2010).

Neuronal hearing loss protection

Mechano transduction ability demonstrated by intact cochlea, auditory brainstem response (ABR), and distortion product optoacoustic emissions (DPOAE) amplitude in mice were measured to evaluate effects of Arctigenin on gentamicin (GMC)-induced neuronal hearing loss. Arctigenin increased survival, neurosphere formation, neuron differentiation of NSCs in mouse cochlear in vitro. Arctigenin also promoted the outgrowth of neurites, as well as neural excitability of the NSC-differentiated neuron culture. Additionally, Arctigenin rescued mechano-transduction capacity, restored the threshold shifts of ABR and DPOAE in our GMC ototoxicity murine model. This study supports protective function of arctigenin in the therapeutic treatment of neuropathic hearing loss in vivo (Haung *et al*., 2017).

Anti-Japanese encephalitis activity

Japanese encephalitis is a neuro-inflammatory disease. Neuro-inflammation is associated with neuronal cell death and various neurodegenerative diseases. Studies suggested that arctigenin inhibited neuro-inflammation induced by over activated microglia by suppressing NO production, expression of iNOS and COX-2, activation of MAPKs and secretion of pro-inflammatory cytokines. Moreover, arctigenin also significantly reduced neuronal cell death. Arctigenin reduced neuronal death and secondary inflammation and oxidative stress resulting from microglial activation in mice with Japanese encephalitis (Swarup *et al.*, 2008; Park *et al* 2011)

Inhibition of Human T lymphocytes proliferation

Arctigenin inhibits primary human T lymphocytes proliferation activated by anti-CD3/CD28 Ab. Arctigenin suppressed interleukin-2 (IL-2) and interferon-γ (IFN-γ) production in a concentration-dependent manner. Furthermore, Arctigenin decreased the IL-2 and IFN-γ gene expression in primary human T lymphocytes induced by anti-CD3/CD28 Ab. Reporter gene analyses revealed that Arctigenin decreased NF-AT-mediated reporter gene expression (Tsai *et al*., 2011).

Anti HIV activity

Arctigenin showed anti-HIV activity primarily due to inhibition of HIV proviral DNA (Eich *et al.,* 1996).At a concentration of 0.5 microM, (-)-arctigenin inhibited the expression of HIV-1 proteins p17 and p24 by 80-90%. The reverse transcriptase activity in the culture fluids was reduced by 80-90% when the cells (HTLV-III B/H9) were cultivated in the presence of 0.5 microM (-)-arctigenin. At the same concentrations, the formation of syncytia in the HTLV-III B/H9-Jurkat cell system was inhibited by the compounds by more than 80%.Studying the molecular mechanism of action of arctigenin it was found that both compounds are efficient inhibitors of the nuclear matrix-associated DNA topoisomerase II activity, particularly of the enzyme from HIV-1-infected cells (Barkat *et al.,* 2014).

Alleviation of ER stress

In a study Arctigenin, has been reported to alleviate ER stress.ER stress has been thought to play a central role in the pathogenesis of type 2 diabetes not only because of its role in the induction of insulin resistance but also because of its involvement in β-cell death, a common feature of type 2 diabetes. Therefore, compounds that alleviate ER stress may act as therapeutic agents for the treatment of β-cell loss in type 2 diabetes. ATG arctigenin is an effective ER stress alleviator, which protects cells against ER stress through activating AMPK, thus attenuating protein translation and reducing ER load (Gu *et al*., 2012).

In Alzheimer's disease

Alzheimer disease is characterized as a progressive neurodegenerative disorder of the brain and leads to irreversible loss of intellectual ability. The β-amyloid (Aβ)-induced neurodegeneration is believed to be the main pathological mechanism of Alzhemier disease. Arctigenin can inhibit Aβ production by suppressing β-site amyloid precursor protein cleavage enzyme 1 expression and promote Aβ clearance by enhancing autophagy through AKT/mTOR signaling inhibition and AMPK/Raptor pathway activation as investigated in cells and APP/PS1 transgenic AD model mice. This result supports arctigenin as potential drug for alzheimer's disease (Zhu *et al*., 2013)

Conclusion

On the basis of above study it is reported that arctigenin is a phytochemical with great potential against a variety of human ailments. Its pharmacological properties have been well studied in recent years.The molecular mechanism of each of these potential effects has to be explored. All the results indicate that arctigenin may be used as an effective therapeutic agent to prevent gastric ulcers, neurological diseases, cancers, potential therapeutic agent for Parkinson's disease etc. Arctigenin is identified as tumor specific agent that showed cytotoxicity to lung cancer, liver cancer, ovarian cancer and stomach cancer cells. This study found that arctigenin is one of cancer specific phytochemicals and responsible for the tumor selective cytotoxicity of the herbal medicine. Considering the

overall benefits of this plant based lignan it can be advocated as an important medicinal compound.

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