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Biological Effects of Arctiin from Some Medicinal Plants of Asteraceae Family

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Abstract

Arctiin is a lignan found in many plants of the Asteraceae family that have had various biomedical applications for many years. Arctiin possesses various biological features such as antiinflammatory, antioxidative, antiproliferative, and antitumor effects. The present review will discuss reports on biological activities of arctiin from 1984 onwards.

Keywords

Asteraceae, Arctiin, Biological Activity, Bioactive Compound

1. Introduction

Detecting therapeutic powers in plants is an ancient idea [1]. World Health Organization (WHO) has reported still about 80% of the world population depends mainly on plant-based drugs. Ayurveda, Siddha, Unani and Folk (tribal) medicines are the major systems of indigenous medicines[2]. Drugs of plant origin applied in the traditional medicine have paid close attention because it is easily accessible, less expensive and also nearly have no side effects [3]. Plants are able to make a vast range of phytochemical compounds as secondary metabolites. Numerous phytochemicals have been consumed effectively for curing various diseases. World Health Organization has identified all medicinal plants used globally and organized them in more than 20,000 species. Most of the medicinal plant parts due to having different medicinal effects are consumed as raw drugs [4]. Many drugs that have used in traditional medicine for curing chronic and even infectious diseases, were producing by plants [5].Today, many studies also perform on biological effects of plant extracts and compounds. For example, the bracken fern extract showed antitumor and antiproliferative effects with inducing apoptosis pathway and cell cycle arrest [6]. However, a plant extract may possess numerous effective compounds that under different conditions show various effects like Bracken fern extract that has multiple effects under *in vivo* and *in vitro*[7]. Infact, there is a need for further studies on standardization or chemical characterization of the extracts used. Hence, investigating plant compounds is more preferable to the extracts. Asteraceae has known as the largest family of flowering plants, with approximately 1620 genera and more than 23,600 species [8]. It is widely distributed within various regions ranging from the southwestern United States, Mexico, and southern Brazil to South Africa, middle and southwestern Asia, and Australia [9]. The Asteraceae species have been introduced as they are a source of numerous biologically active compounds like essential oils [10-13], polyphenolic compounds [14-20], terpenoids [17-19, 21-24], phenolic acids [16, 19], alkaloids [25], lignans, saponins [17, 23], stilbenes, sterols [19], polysaccharides [21] and many others, Because plants bio-active properties from Asteraceae family are commonly used in treatment of diverse diseases. Arctiin (chemical structure seen in Fig. 1) is a lignan that detected in many plants of the Asteraceae family, particularly the greater burdock (*Arctiumlappa*) and *Centaureaimperialis*, and in *Trachelospermumasiaticum*, *Saussureaheteromalla* [26], and *Forsythia viridissima* [27]. Moreover arctiin contains many kinds of bioactivities [28] and a number of imperative pharmacological effects including desmutagenic, cytotoxic [29, 30], antiproliferative [31, 32], anticarcinogenesis [33],

platelet activating factor antagonistic [34] and calcium antagonistic [35] activities. The main objective of this review is to focus on arctiin with biological activities, reported in the time period of 1984 to 2016. The biological properties of arctiin were categorized as follows: antiinflammatory, antiproliferative-cytotoxicity-antisenescence,antioxidative, antitumor, toxicity, antidiabetic, antiadipogenic, antibacterial, UVB protective effect, Influenza therapeutic agent, and other biological activity.

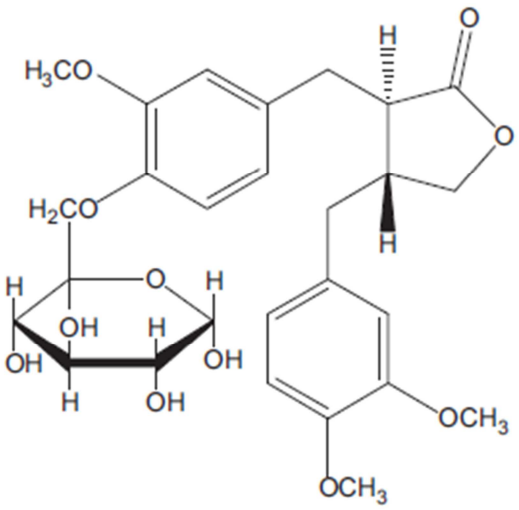

Figure 1. *Chemical structure of arctiin [36].*

2. Anti-inflammatory Activity of Arctiin

The finding demonstrated that arctiin largely inhibited the excessive production of inflammatory mediators such as nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor (TNFa), interleukin 1-beta (IL-1 b) and interleukin 6 (IL-6) as well as the suppression of cyclooxygenase-2 (COX-2) through the inhibition of nuclear factor (NF)-kB translocation pathway [37]. Lee and et al proved that arctiin inhibits the expression of co-stimulatory molecules such as B7-1 and B7-2; and activation ofnuclear transcription factor (NF)-kB in macrophages. The studies provide evidence of the bioactivity of arctiin in inflammatory diseases. As a matter of fact, they showed that arctiin has antiinflammatory effects on macrophages through the reduce pro-inflammatory cytokines are associated with NF-kB inactivation and the suppression of NF-kB-regulated proteins, and other bioactive substances as well as through inhibition of the expression of co-stimulatory molecules [37].

3. Anti-Proliferative-Cytotoxicity-Anti-Senescence Activity of Arctiin

Bae, Lim [38] studied on human hair dermal papilla cells (HHDPCs) in the presence of arctiin and/or Hydrogen peroxide (H_2O_2) to determine whether H_2O_2-induced cell dysfunction could be stopped by arctiin treatment. The findings showed that arctiin induces cytotoxicity in HHDPC. Also, it inhibited H_2O_2-mediated cell proliferation loss in dose-dependent manner in HHDPCs. Infact, arctiin decreased H_2O_2-mediated cytotoxicity in the cells [38]. Furthermore, they reported that arctiin inhibits H_2O_2-mediated cell death and cell cycle arrest in these cells. Arctiin was remarked that decrease the accumulation of cells treated with H_2O_2 in sub-G1, S, and G2/M phases in a dose-dependent manner [38]. Arctiin inhibite hydrogen peroxide-mediated sub-G1 accumulation that is indicative of dead cells. Also, the proportion of G2/G1 cells was increased by H_2O_2 treatment in compared with untreated control cells. This result showed that H_2O_2 induce G2 arrest in HHDPCs. However, the proportion of G2 arrest cells was considerably attenuated by arctiin pretreatment. These results indicated that arctiin blocks H_2O_2-mediated cell death and G2 arrest in HHDPCs. In addition, Arctiin inhibits H_2O_2-mediated ROS generation in HHDPCs [38]. ROS generation mediated by H_2O_2 is characterized by increases in cell death and cell cycle arrest in several cell lines [39]. Bae, Lim [38] demonstrated that arctiin does not alter intracellular ROS levels in untreated control cells, but it significantly obsolete the H_2O_2-induced increase in intracellular ROS generation. Moreover, arctiin inhibits H_2O_2-mediated senescence in HHDPCs. Cell cycle arrest in the G2 phase and Reactive Oxygen Species (ROS) generation are functionally connected with cellular senescence [40, 41]. Peroxide hydrogen treatment enhanced the percentage of senescent cells by 24.89% compared with untreated control cells. Although, 20 μM arctiin pretreatment the percentage of senescent cells by 10.89% compared with H_2O_2-treated cells. Infact arctiin negatively adjusts H_2O_2-mediated senescence in HHDPCs (Fig.2). Besides, Arctiin modifies H_2O_2-mediated changes in miRNA expression [38]. miRNAs are main small non-coding RNA molecules, and applies their biological functions by post-transcriptionally redacting to their target genes [42, 43]. These findings indicated that arctiin regulates the expression levels of special miRNAs in HHDPCs. The data showed that arctiin has a protective effect against H_2O_2-induced cellular senescence and apoptosis in dermal papilla cells. The modified miRNAs may be involved in regulating pathways of cancer, cell cycle, and Wnt and Mitogen-activated protein kinases (MAPK) signaling, among others. Overall, the results indicated that the protective effects of arctiin against H_2O_2-induced alterations in HHDPCs may be regulatedby arctiin-specific miRNAs and pathways that are probably influenced by miRNAs [38]. Matsuzaki, Koyama [44] examined the effect of arctiin on the proliferation of human immortalized keratinocyte HaCaT cells. The findings showed that Arctiin inhibits the growth of HaCaT cells in a dose-dependent manner. Also they indicated that arctiin down-regulates the expression of cyclin D1 protein in a time-and dose-dependent manner. As a matter of fact arctiin induces growth inhibition is correlated with the arctiin-induced down-regulation of cyclin D1 protein, While they showed that arctiin slightly affects the amount of cyclin D1 mRNA [44]. This result suggested that arctiin post-transcriptionally down-regulates

the cyclin D1 protein expression. Moreover they found that arctiin slightly reduces amount of retinoblastoma protein (RB) protein in HaCaT cells and it leads to RB protein band shift from a hyperphosphorylated form to a hypophosphorylated form. These results indicated that arctiin dephosphorylates RB protein in HaCaT cells [44]. The studies proved that down-regulation of cyclin D1 by arctiin is a general event. As arctiin inhibits the expression of cyclin D1 protein in osteosarcoma cell line MG63, the lung cancer cell line A549, the colorectal cancer cell line HCT116, the cervical cancer cell line HeLa, the breast cancer cell line MCF7, the melanoma cell line UACC-62, the human transformed renal cell line 293T and the prostate cancer cell line DU145. The arctiin-induced down-regulation of cyclin D1 protein is a ubiquitous event in human tumor cells. Also, cyclin D1 is one of the key targets of arctiin for its growth inhibitory function [44]. Yoo, Lee [45] investigated anti-proliferative effects and ability of arctiin and 2 other lignans in habiting Wnt/B-catenin signaling in SW480 human colon cancer cells. The lignans stop SW480 cell growth. Moreover, the transcriptional activities of a reporter constructcomprising the TCF binding element (TBE) was decreased after the treatment with arctiin.

Huang, Guh [46] examined the arctiin effects on growth regulation in prostate cancer PC-3 cells. They found that in serumfree conditions, arctiin do not have any effects even at a high concentration. Although, in serum-containing conditions, cell growth inhibition occurred following a 42hr treatment with arctiin; the mechanism of action appeared to be through an anti-proliferative effect. However, treated cells with arctiin considerably showed cytotoxic effect in addition to antiproliferative effect during 48h which was concentration-dependent.

However, after the microscopic observation, it was clear that arctiin induced cell detachment from culture plates in a concentration-dependent manner. In point of fact, arctiin had little cytotoxic effect. The leading cause of decline in the number of PC-3 cells following arctiin treatment was arctiin effect on cell detachment other than a direct effect. Huang, Guh [46] showed that protein synthesis is required for the arctiin-mediated cell detachment effect. Arctiin increased the expression of the anti-adhesion mucin MUC-1, but did not affect integrin expression in PC-3 cells. The arctiin induces increasing of MUC-1 protein expression because of up-regulation of mRNA, as revealed by RT-PCR analysis [46]. Also, Shoeb, Macmanus [47] showed that none of the plant extracts that contain Arctiin, revealed any significant cytotoxicity against the CaCo-2 colon cancer cell line. While isolated biocompound, arctiin, and showed remarked cytotoxicity [47]. The previously studies indicated that it is not at all surprising to have active agents from inactive extracts or fractions as the amounts of active agents present in the amounts of extracts or fractions examined,can be too small to show any activity[47]. The studies demonstrated that arctiin has cytotoxicity effect on LNCaP prostate cancer cells [48]. These effects (antiproliferative and cytotoxicity) were proved in other studies also [31, 32]

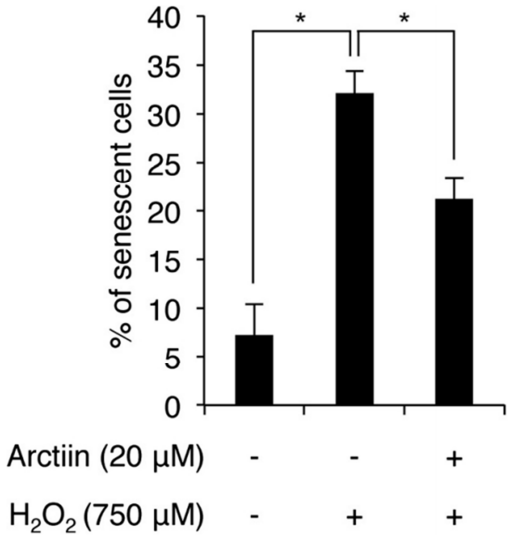

Figure 2. *Effect of arctiin on Hydrogen peroxide-induced senescence as measured by SA-β-gal assays. HHDPCs were pre-treated with DMSO or arctiin (20 μM) followed by H_2O_2. The graph indicates the mean value of senescent (SA-β-gal stained) cells from three independent experiments. *p < 0.05 compared with H_2O_2-treated HHDPCs (Bae et al., 2014).*

4. Antioxidative Activity of Arctiin

The studies showed that increase in cell death and cell cycle arrest in cell lines may lead to ROS generation mediated by H_2O_2 [39]. Bae, Lim [38] investigated arctiin effects on H_2O_2-mediated ROS generation. Arctiin significantly overthrow the H_2O_2-induced increase in intracellular ROS generation in HHDPCs, However, it do not alter intracellular ROS levels in untreated control cells [38]. Shoeb, Macmanus [47] investigated antioxidant activity of extract of some plant from Centaurea species that were shown arctiin present in these extract. The crude extracts showed important levels of free radical scavenging activity (antioxidant activity) in the DPPH assay that was because of the presence of arctiin and other compound with significant antioxidant effects.

5. Anti-Tumor Activity of Arctiin

Takasaki, Konoshima [49] reported that arctiin has a significant inhibitory effect as seen in a two-stage carcinogenesis test of mouse skin tumors induced by 7,12-dimethylbenz[α]anthracene (DMBA) and 12-*O*tetradecanoylphorbol-13-acetate (TPA). Hirose, Nishikawa [50] showed that arctiin has remarkable protective effects on 2-amino-1-methyl-6-phenylimidazo[4,5-ß]pyridine (PhIP)-induced carcinogenesis in colon, pancreatic, and particularly in the mammary gland during the promotion period. In addition, arctiin induces growth inhibition in human prostate cancer PC-3 cells and that it is associated with up-regulation of the anti-adhesion mucin MUC-1 gene [46]. Also, Hirose, Yamaguchi [33] demonstrated anticarcinogenesis effect of arctiin in their studies.

6. Toxicity Activity of Arctiin

According to obtained results in 2006, arctiin did not have any toxic effect against shrimp larvae. It is well known fact that anticancer drug's therapeutic doses may produce toxic side effects because of their cytotoxicity and poor selectivity between target and normal cells. It has been showed that arctiin can be as a well-known anticancer agent without having any toxicity effect [51]. However, Shoeb, Macmanus [47] following previous studies, investigated general toxicity effect of extract of some plants on colon cancer cell lines. The findings showed that the extract has toxicity effect that arctiin is one of the major components that present in the extract [47]. Also other studies proved that arctiin has considerable toxicity [51, 52].

7. Anti-diabetic Activity of Arctiin

Ma, Liu [53] investigated the potential effect and mechanism of arctiin on streptozotocin (STZ)-induced experimental Diabetic nephropathy (DN) in rats. The results indicated that the size of glomeruli in diabetic rats is larger with increasing Kidney International (KI) and the main constituent of GFB (glomerular filteration barrier)-GBM (glomerular basement membrane) is thicker than those in control rats. Treatment with arctiin leads to size of glomeruli significantly decreased and restored the impaired structure of glomeruli. Also, both the gene and protein expression of nephrin and podocin were lessenedmarkedly in diabetic rats. Treatment of arctiin ameliorated the diabetes-induced nephrin and podocin depletion [53]. These studies howed that the gene and protein expression of heparanase are increase significantly in diabetic rats and administration of arctiinreduces the diabetes-induced heparanase up-regulation. Arctiin largely restore the GFB damage in STZ-induced diabetic rats through up-regulating the expression of nephrin and podocinand down-regulating HPSE level. Therefore, arctiin may use as new case for treatment of DN [53]. Moreover, other studies investigated the effect of arctiin on serum glucose and HBA1c levels, the blood viscosity, and VEGF expression in the retinal tissues of rats with diabetic retinopathy. The glycosylated haemoglobin (HBA1c) level was significantly reduced in all of the arctiin-treated groups when compared with the control group, and the serum glucose level was also lessened in the rats treated with the highest dose of arctiin. In addition, treatment with arctiin ameliorated retinal oedema, detachment of the retina, and VEGF expression in the retina, as detected using histological and immunochemical examinations[54]. Arctiin increases the viability of retinal microvascular endothelial cells in vitro. These findings demonstrated that arctiin attenuates the intensity of diabetic complications, demonstrating the significance of this compound as an inhibitor of diabetic retinopathy [54]. According to obtained results, arctiin has ameliorative effects on cationic bovine serum albumin (cBSA)-induced glomerulonephritis in rats. The findings showed that after oral administration of arctiin, the levels of serum creatinine (Scr) and blood urea nitrogen (BUN) and 24-h urine protein content significantly decrease, while endogenous creatinine clearance rate (ECcr) considerably increases [36]. The parameters of renal lesion, hypercellularity, infiltration of polymorphonuclear leukocyte (PMN), fibrinoid necrosis, focal and segmental proliferation and interstitial infiltration, were reversed. In addition, arctiin evidently decreased the levels of malondialdehyde (MDA) and proinflammatory cytokines includinginterleukin-6(IL-6) and tumor necrosis factor (TNF-a), repressed nuclear factor-kB p65 (NF-kB) DNA binding activity, and increased superoxide dismutase (SOD) activity. One of the probable mechanisms for these results is that arctiin, after transformation into arctigenin, suppresses NF-kB activation and nuclear translocation, followed byattenuates in the levels of these pro-inflammatory cytokines, while SOD is involved in the inhibitory pathway of NF-kB activation. According to obtained results that arctiin has desirable potency for the development of an inhibitory agent of NF-kB and further application to clinical treatment of glomerulonephritis, though clinical studies are required [36].

8. Anti-adipogeneic Effect of Arctiin

Min, Lee [55] examined the effects and associated mechanisms of arctiin on adipogenesis in 3t3-l1 cells. The findings showed that 3T3-L1 cells pre-adipocytes treated with arctiin significantly reduce adipogenesis in a dose-dependent manner. The protein levels of the key adipogenic regulators Peroxisome proliferator activated receptor γ (PPARγ) and CCAAT/enhancer binding protein α (C/EBPα), considerably decrease by arctiin treatment [55]. Also arctiin significantly stops the expression of Sterol regulatoryelement-binding transcription factor 1 (SREBP-1c), fatty acid synthase, fatty acid-binding protein and lipoprotein lipase. The phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target phosphorylated-acetyl CoA carboxylase extremely increase by arctiin. Administration of arctiin significantly decreases the body weight in obese mice fed with the high-fat diet. Also it reduces the sizes of lipid droplets in the epididymal adipose tissue [55].

9. Anti-bacterial Activity of Arctiin

Studies showed that arctiin does not have any significant antibacterial activity against both Gram-positive (*S. aureus, M. lateus, B. cereus*) and Gram-negative bacteria (*E. coli, P. aeroginosa*) when compored with the positive control agent chloramphenicole [56].

10. Arctiin Transformation to Other Compounds by Bacteria

The findings showed that arctiin transforms by human and rat intestinal bacteria to different compounds such as (-)-

arctigenin, (-)-enterolactone and butyrolactone derivatives [57]. In fact, bacteria may transform the arctiin into compounds with no antibacterial activity [58].

11. UVB Protective Effect of Arctiin

The studies showed that a low dose of arctiin has UVB protective activity in normal human dermal fibroblast (NHDF) cells. They also demonstrated that arctiinstops the UVB-mediated cell growth defect, apoptosis, cell migration defect and DNA damage in these cells. Arctiin-induced UVB protection is related to modifiedmicroRNA (miRNA) expression[59]. Moreover, Human HaCaT keratinocytes treated with arctiin are protected from UVB-mediated damage. Biochemical assays revealed that UVB-induced cytotoxicity and cell death are significantly decreased in arctiin-pretreated HaCaT cells. In addition, arctiin promotes the wound healing and DNA repair properties of keratinocytes [60]. The findings indicated that the photoprotective effects of arctiin are associated with changes in the expression levels of specific microRNAs (miRNAs) in HaCaT cells [60]. A bioinformatics analysis demonstrated that the miRNAsare functionally involved in cancer, cell cycle, and Wnt and mitogen-activated protein kinase (MAPK) signaling pathways [59].

12. Arctiin as Influenza Therapeutic Agent

Hayashi, Narutaki [61] showed that arctiin is an influenza therapeutic agent, involving the protection from lethal influenza virus (IFV)-infection, inhibition of viral replication, increased immune response, low frequency of drug resistant virus generation and increased antiviral efficacy with oseltamivir, a neuramidase inhibitor. The stability of arctiin was proved because it was detected for a longer time, over 12 h, in the blood of mice administered orally with it [61]. As a matter of fact, Arctiin was orally efficient against either Influenza virus (IFV)-inoculated normal or 5-fluorouracil (5-FU)-treated mice, being less efficient as compared with oseltamivir. Arctiin produced more amount of virus-specific antibody than those of control and oseltamivir in sera collected from 5-FU-treated mice. Furthermore, oral treatment of 5-FU-treated mice with arctiin did not induce any resistant viruses, however the oseltamivir treatment in the same condition induced resistant viruses at a 50% frequency. When normal mice infected with IFV, treated with the combination of arctiin and oseltamivir, the virus yields in both bronchoalveolar lavage fluids and lungs were considerably decreased relative to those in the mice treated with arctiin or oseltamivir alone. Therefore, arctiin biocompounds and or combination of arctiin with Osetamivir can use as potent agents in influenza treatment [61].

13. Other Biological Activities

Shilova, Semenov [62] demonstrated arctiin contains marked nootropic activity that was comparable with that of the whole CHCL3 fraction of the extract of Alfrediacernua (L.). The studies proved that arctiin also has antiparasiticactivity. As it exhibited significant activities against *D. intermedius* (Monogenea) in goldfish (Carassiusauratus) [63]. It has desmutagenic effects also [29, 30]. Investigations showed that arctiin is a platelet activating factor antagonist [34] that activity of calcium antagonist of it proved also [35].

14. Conclusion and Perspective

Vast group of medicinal plants are used in traditional medicine, which have potential to treat different diseases. Since the last decade, there has been remarkable attention into potential biological effects of the plant of Asteraceae family. It is assume that arctiin is a potential bioactive that contains many biological activities. However, there is a need for further studies on biological activities of arctiin. Also, mechanism of arctiin in many of biological effects is unknown. Therefore, much effort is expected in identifying arctiin effects and mechanism action to use it for therapy of certain diseases. Also, it would be the subject of considerable interest in the future to investigate whether the biological activities of arctiin will enhance in combination with other available agentspossesses biological effects such as anticancer, antibacterial, anti-inflammatory and etc. It is ultimately suggested that according to the various biological activities of arctiin, this compound may has even a wider range of biological usage in the future.

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