Withaferin A has shown significant anti-cancer activity in animal studies

Withaferin A has been extensively studied for

1. **Anti- inflammatory**
2. **Anti- tumor**
3. **Anti-angiogenesis**
4. **Radio sensitizing activity**
5. **Chemo preventive and**
6. **Immunosuppressive activities**

1. ANTI-INFLAMMATORY ACTIVITY:

The anti-inflammatory effect of withaferin A on a experimental mice model for gouty arthritis monosodium with urate crystal induced inflammation was studied. A cellular model of cystic fibrosis inflammation was established by Maitra et al to assess the anti-inflammatory activity of withaferin A [1,2]

2. ANTI-TUMOR AND RADIOSENSITIZING ACTIVITY:

Shohat et al first reported the anti-tumor activity of withaferin A in 1967 [3]. They also studied the effect of withaferin A on Ehrlich ascites tumor cells [4, 5]. Sharada et al confirmed the anti-tumor effect of withaferin A against mouse Ehrlich ascites carcinoma cells. In addition, radiosensitizing effect of withaferin A was first demonstrated and an optimum dose of 30 mg/kg withaferin A in combination with 7.5 Gy gamma radiation for Ehrlich ascites implanted mice was demonstrated by Devi et al [6,7]. The anti-tumor and radiosensitizing activities of withaferin A were tested for different cancer cell lines. Devi et al evaluated the radiosensitizing effect of withaferin A on B16F1 mouse melanoma cells and mouse fibrosarcoma grown in C57B1 and swiss albino mice[8,9]. Kalthur et al confirmed that withaferin A, hyperthermia and irradiation acted synergistically against B16F1 melanoma and withaferin A served as a better radio sensitizer than hyperthermia [10].

The anti-tumor effect of withaferin A against human prostate cancer cell lines was tested. Withaferin A exhibited androgen receptor (AR) dependent cell killing against prostate cancer cell lines [11]. It was confirmed in PC-3 xenografts in nude mice. Withaferin A was also demonstrated to inhibit HSP 90 by directly binding to the C-terminus, which was different from classical HSP 90 inhibitors and thus proposing a new mechanism for developing HSP 90 inhibitors. Combined withaferin A with myricetin enhanced anti-cancer efficacy in pancreatic cancer cells. Withaferin A 6 mg/kg inhibited tumor growth in pancreatic panc-1 xenografts [11A].

Stan et al demonstrated that withaferin A inhibited proliferation of breast cancer cells with IC 50 s of 1.5 µm for MCF-7 cancer cells and 2.0µm for MDA-MD-231 cancer cells[12].

Withaferin A exhibits anti-proliferative activity against human promyelocytic leukemia cells HL-60, U937, lymphoid origin human T-(MOLT-4, Jurkat), B-(REH) cells and myeloid origin K-562 leukemic cells, but not the normal lymphocytes peripheral blood mononuclear cells(PMC)[13,14,15].

Withaferin A inhibited cell survival in three human colon cancer cell lines SW-480, SW-620 and HCT-116 without affecting normal colon epithelial FHC cells [16].

The anti-proliferative activity of withaferin A was demonstrated against human head and neck squamous cell carcinoma UM-SCC-2, MDA 1986, JMAR & JHVO 11 [17].

3. ANTI-ANGIOGENESIS ACTIVITY:

Anti-angiogenesis activity of withaferin A was first demonstrated by Mohan et al [18]. Withaferin A was shown to inhibit human umbilical vein endothelial cell (HUVEC) sprouting in three –dimensional collagen-1 matrix, inhibit HUVEC cell proliferation with IC50 of 1.2 nM and exert potent anti-angiogenic activity in FGF-2 matrigel plug angiogenesis mice model at doses as low as 7µg/kg/day which were 500 fold lower than the reported doses to exert anti-tumor activity in vivo. Withaferin A significantly inhibited neovascularization in injury-induced carneal neovascularization mouse model by about 70% [19].

4. CHEMOPREVENTIVE ACTIVITY:

Chemopreventive role of withaferin A was demonstrated. It was shown that 7, 12-dimethyl benz[a] anthracene (DMBA) induce oral carcinogenesis in syrian golden hamsters, Where as oral administration of 20 mg/kg withaferin A could completely prevent the tumor induction by DMBA [20, 21].

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STRUCTURE ACTIVITY RELATIONSHIP OF WITHAFERIN A AND ITS PHARMACOLOGICAL ACTIVITY:

The key structural components in withaferin A which contribute to its biological activities were elucidated.

Withaferin A is highly reactive towards proteins as the ketone containing unsaturated A ring (Double bond at C2-C3 Position), the epoxide ring within B ring and unsaturated lactone ring were all demonstrated to be involved in Michael addition, thioalkylation reactions. The double bond in ring A is crucial for the cytotoxicity of withaferin A. The double bond dissociated derivatives of withaferin A showed little cytotoxicity. Where as the C27 hydroxyl group and the α,β-unsaturated δ-lactone ring (Double bond at C24-C25) are not required for the cytotoxicity of withaferin A. 5β,6β-epoxide ring is crucial for its cytotoxicity . The conjugated ketone carbon in the ring A is required for the proteasome inhibition. The C2-C3 unsaturated position of the A ring and C5-C6-epoxide group contributes to the binding of withaferin A to vimentin. Whereas withaferin A derivatives 3β-methoxydihydrowithaferin A (or) thiophenoxydihydrowithaferin A (Without C2-C3 double bond) failed to inhibit vimentin [1-5].

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STRUCTURAL MODIFIED DERIVATIVES OF WITHAFERIN A:

Yokota et al developed a biotinylated affinity analogue of withaferin A for use as a probe to study angiogenesis[1].

A library of 2, 3-dihydro-3β-substituted withaferin A derivatives were prepared by regio/stereoselective Michael addition to ring A. The analogues were tested for in vitro cytotoxicity against various human cancer cell lines. 3- Azido analogue exhibited 35 fold increase in cytotoxicity against all cell lines compare to parent molecule[2].

A series of withaferin A analogues were prepared and tested for its activity in proliferative diseases, neurodegenerative diseases, autoimmune and inflammatory diseases[3].

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DEVELOPED A PATENTED (India Patent Application No. 55/CHE/2011***) PROCESS TO ISOLATE BULK QUANTITIES OF WITHAFERIN A. WE CAN MEET ANY QUANTITIES OF INDUSTRIAL REQUIREMENTS WITH PURITIES >98% BY HPLC.***

FOR FURTHER DETAILS PLEASE FEEL FREE TO CONTACT xenonbiosciences@gmail.com / withaferina@gmail.com / (OR) +91-9849601776