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ALTHOLACTONE: A NATURAL LEAD SCAFFOLD AS A POTENTIAL ANTICANCER AGENT

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ABSTRACT: Cancer is one of the most dreaded diseases across the globe. Drug resistance and adverse effects of various classical chemotherapeutic agents are the major challenges for cancer therapy. Cancer treatments with synthetic drugs are associated with severe side effects. Synthetic drugs address symptoms caused by diseases; on the other hand a plant-based medicine usually directs towards aiding body's own healing process as it is in sync with nature. Natural products and their derivatives can be a promising alternative to existing cancer therapy. Several phytoconstituents have been identified as a valuable source of clinically important anticancer agents. Novel chemical entities and compounds of natural origin have been explored for efficient anticancer activity. Altholactone, a styryl lactone primarily found in *Goniothalamus* sp., exhibits cytotoxic and antitumor activities. Therefore, an attempt has been made to summarize altholactone analogues. Its structure-activity relationship (SAR) is suggested as a potent anticancer drug candidate, which may provide a structural framework to design and develop a novel anticancer drug in the future.

INTRODUCTION: Cancer is the second most leading cause of death globally and is responsible for 9.6 million deaths in 2018 worldwide [1]. According to WHO, a cancer mortality rate of 79 per 100,000 deaths was reported in India, and this accounted for 6 percent of total deaths [2]. Most anticancer agents lack selectivity against cancer cells, display a narrow therapeutic index and drug resistance. A search of a potent drug candidate for treatment and minimizing their toxic side effects in cancer treatment is the need of the hour [3].

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Over the past half-century, small organic molecules derived from plants have been employed for cancer chemotherapy [4]. These phytoconstituents exhibit considerable structural diversity, tend to adopt preferred conformation and necessary steric complexity compared to other synthesized organic compounds. Phytoconstituents have more chiral centers, less hetero, and heavy atoms with complex ring systems. Therefore, the natural products are regarded as possessing "drug-like" and "biologically friendly" molecular properties [5-7]. Natural products act as good lead compounds for optimization by chemical modification through synthetic organic chemistry methods in the discovery of anticancer agents.

Goniothalenol or altholactone (1) belongs to the styryl-lactone family; it comprises of an α,β-unsaturated δ-lactone (5-oxygenated- 5,6-dihydro-

2H-pyran-2-one) and a disubstituted furanic motif with a cis configuration bicyclic ring system. IUPAC nomenclature of (+) altholactone nucleus is (2R,3R,3aS,7aS)-3-hydroxy-2-phenyl- 2, 3, 3a, 7a-tetrahydrofuro [3, 2-b] pyran-5-one **Fig. 1**. (+)-Altholactone is characterized by the presence of a cis-fused tetrahydrofurano-2 pyrone structure and its diastereomer, isoaltholactone **(3)**, differs only in the configuration of the stereogenic centers at C-2 and C-3. Styryllactones are found primarily in *Goniothalamus* sp., and have various cytotoxic and antitumor activities [8]. In the review, we have summarized the current knowledge including their isolation, synthesis and structure activity relationship (SAR) of altholactone and its derivatives as anticancer agent.

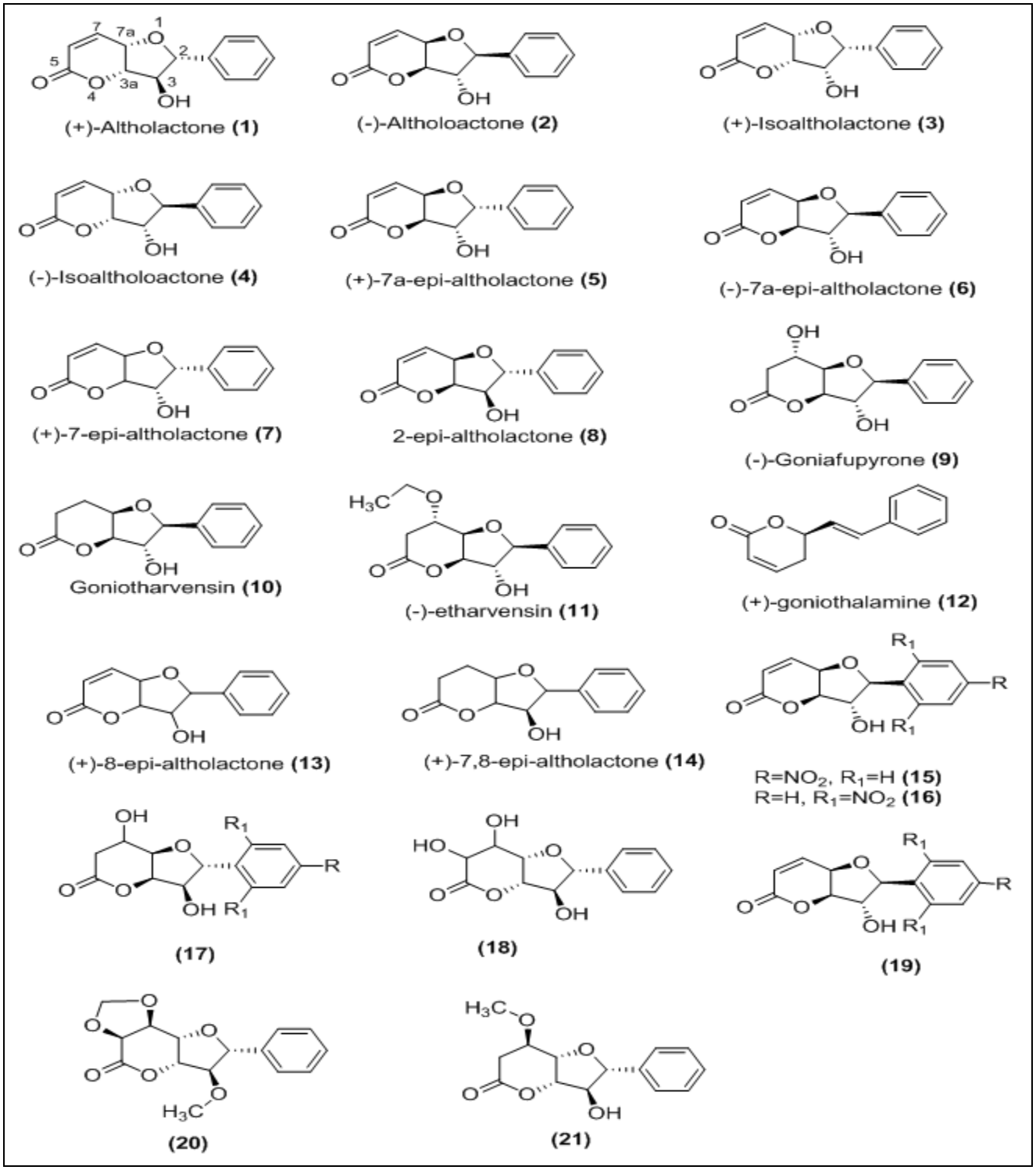

FIG. 1: STRUCTURE OF αβ-UNSATURATED FURANO(ALTHOLACTONE TYPE) AND RELATED COMPOUNDS

1. Sources of Altholactone: Loder and Nearn in the year 1977, identified altholactone from the bark of *Polyalthia* sp., [9]. Later after eight years El-zayat et al isolated it from the bark of *Goniothalamus giganteus* (Annonaceae) [10]. (+)-Altholactone **(1)** was characterized from *G. arvensis Scheff*., and *G. borneensis* collected in Malaysia [11-12]. (+)-Isoaltholactone (3) was isolated from the stem bark of *G. malayanus*, stem bark and leaves of *G.montanus* and roots of *G. tapics* [13] **Table 1**.

TABLE 1: ALTHOLACTONE AND ITS DERIVATIVES FROM GONIOTHALAMUS SPECIES

S. no.	Name of plant	Constituents	Source	Reference
1	*Goniothalamus giganteus*	(+)-altholactone (+)-Isoaltholactone	Stem bark and leaves	[10, 18]
2	*Goniothalamus montanus*	(+) -Isoaltholactone	Leaves	[13]
3	*Goniothalamus tapis*	(+) -Isoaltholactone	Root	[13]
4	*Goniothalamus arvensis*	(+)-altholactone (+)-isoaltholactone (+)-goniotharvensin	Stem bark	[14, 15]
5	*Goniothalamus fasciculatus*	(+)-altholactone	Stem bark	[16]
6	*G. maiayanus*	(+)-altholactone	Stem bark	[16]
7	*Goniothalumus borneensis*	(+)-altholactone	Bark	[12]
8	*Goniothalamus macrocalyx*	7-acetylaltholactone	Fruits	[17]
9	*Goniothalamus griffithii*	(+)-altholactone, isoaltholactone	Rhizome, stem	[19,20]
10	*Goniothalamus grandiflorous*	isoaltholactone	Stem bark, leaves and flowers	[21]
11	*Goniothalamus undulatus*	O-acetylaltholactone, altholactone	Root	[22]
12	*Goniothalamus australis*	altholactone	Aerial	[23]

1.1 Biosynthetic Pathway for Altholactone: The furano-pyrone skeleton represents the second most abundant class of styryllactone in *Goniothalamus* sp. These secondary metabolites are derivable from mixed biogenesis involving shikimic acid and acetate pathways [24]. All styryl-lactones were isolated with the same basic C6-C3-C4 skeleton. (+)- goniothalamine (12) is considered as the pivotal precursor. Biosynthesis of stryllactone most probably involves a combination of the shikimic acid derivative cinnamate with two units of acetyl Co A. Subsequent biosynthetic process involves oxidation(s), epimerization(s), ring closure, and rearrangement of the framework, which leads to the full variety of stryllactone scaffolds [25].

1.2 Synthesis of Altholactone: The fascinating structure and the potent bioactivity of altholactone have attracted attention from synthetic chemists from all over the world to design and develop anticancer agents. Several synthetic methods have been employed and modified to get altholactone in high yield.

(+)-Altholactone and its enantiomers have been synthesized from various precursors D-Glucose [26-28], D-mannose [33, 45, 50], D-gulonolactone [29, 33], glyceraldehyde acetonide [30], lactonic aldehyde [32], D-glucoheptanoic γ lactone [36], ethyl-lactol [42], diethyl L-tartrate [38, 43],cinnamyl alcohol [39, 40], tri-*O*-acetyl-D-glucal [46], 2, 3- O- cyclohexylidene-D-glyceraldehyde [48], tetrahydrofurano- 2- pyrone [31], furfural [37], diaxanone [41], dihydrofuran [44], tetra-hydrofuranyl [47], 2-hydroxymethyldihydrofuran [49],γ-lactone intermediate derived from (+)-tricarbonyl (η- 6- o- (trimethylsilyl)benzaldehyde)chromium(0) complex [53] and C-bromofuranosides [54]. Few numbers substituted analogs of altholactone were also synthesized *viz*., aza analogs of isoaltholactone from encarbamate [51] and trifluoromethylated analogue of Isoaltholactone [52].

2. Anticancer Activity of Altholactone: Apoptosis is a programmed mode of cell death; it is a highly regulated process and serves to eliminate unwanted cells. It is characterized by specific morphological features like chromatin condensation and nuclear fragmentation. The apoptotic pathway is activated by extracellular as well as intracellular signals. Cytotoxic T cells are responsible for the generation of extracellular or death-inducing signals from the immune system in response to damaged or infected cells. Fas ligand (Fas-L), tumor necrosis factor (TNF) and TNF-related apoptosis ligands are extrinsic signaling pathways of apoptosis [55].

Intracellular signals (mitochondrial signals) include DNA damage, cytokine deprivation, and growth

factor deprivation. The intracellular pathway is regulated by the B-cell lymphoma-2(Bcl 2) protein family. Various apoptotic signals results in the up-regulation of BH3, which then activates BAX (Bcl-2-associated X protein) and BAK (Bcl-2 homologous antagonist killer). With the onset of apoptosis signals, changes begin to occur within the cells, like activation of caspases (cysteine aspartyl-specific proteases), which is responsible for cleavage of cellular components. Caspases are a class of cysteine protein which are of two type's initiator (caspase-2, 8, 9, 10) and executioner caspases (caspases -3, 6, 7) that are responsible for cleavage of target protein that eventually leads to cell death [56].

Studies have revealed that altholactone and its derivatives induce apoptosis in various tumor cells. Cancer cell lines including prostate cancer cells (DU145) [57], human bladder cancer (T24) [58], leukemia cells L-1210 [59], human small cell lung cancer(NCI-H187) [60], cervical carcinoma HeLa cell [61] have been reported to cause apoptosis by altholactone.

(+)-altholactone, (-)- 3- acetyl- 6, 7- dihydro-altho-lactone, 3-acetyl-6, 7-diacetoxy-6, 7-dihydro-altho-lactone and 3-acetyl-6, 7-dihydro-6, 7-methylen-dioxy-altholactone was isolated from *G. arvensis* Scheff and semisynthetic derivative of altholactone (+)-11-nitro altholactone (15), (+)-9, 13-dinitro-altholactone (16), (+)-6,7-dihydro-7-chloro-altho-lactone (17), (-)-6,7-dihydro-7-methoxy-altholactone were prepared. These compounds were reported to exhibit cytotoxicity in leukemia cells L-1210 [36]. 3-acetylaltholactone and altholactone were isolated from the stem bark of *Goniothalamus arvensis* exhibited cytotoxicity in HL-60 leukemia cells. For altholactone the mechanism of cytotoxicity was based on inhibition of mammalian mitochondrial respiratory chain. 3-Acetylaltholactone showed loss of mitochondrial transmembrane potential, which lead to the release of apoptosis-specific protease activators in HL-60 leukemia cells. This resulted in the activation of apoptosis initiator caspase 9 and executioner caspase 3 and 7 [59]. Altholactone isolated from Malaysian plant *Goniothalamus malayanus* was examined for the mechanism of apoptosis on human HL-60 promyelocytic leukemia cells by Inayat-Hussain *et al*. They reported that apoptosis induced by altholactone was a result of oxidative stress-dependent pathway resulting in loss of mitochondrial transmembrane potential [62].

Altholactone treatment probably results in a reduction of cellular glutathione which may lead to rise of reactive oxygen species (ROS). This alters the redox status of the cells, leading to activation of signaling that will initiate the apoptotic cell death.

Altholactone isolated from *Goniothalamus griffithii* Hook. f. thoms exhibits cytotoxicity on hepatocyte cell lines (HepG2), drug-resistant hepatocyte cell lines (HepG2-R) and primary cultured normal mice hepatocyte. It was observed that altholactone arrested HepG2 and HepG2-R cells in the G2/M phase with different degree [63]. Altholactone isolated from *Gonithalamus laoticus* (Annoneceae) exhibited cytotoxic effect against human epider-moid carcinoma (KB), human breast cancer (MCF-7) and human small cell lung cancer cell lines (NCI-H187) [60]. O-acetylaltholactone and altholactone isolated from the root extract of *Goniothalamus undulatus* and reported cytotoxicity against normal human fetal fibroblast (MRC-5) and large cell lung carcinoma (COR-l23) [61].

Altholactone isolated from *Goniothalamus sp.*, (Annonaceae) hooks were evaluated against colorectal cancer cells (CRC) [65]. It was observed that altholactone induced apoptosis in CRC cells but not in normal fibroblasts. On dissection of the altholactone-induced apoptotic signaling pathway, it was revealed that altholactone activated both caspase-dependent as well as independent apoptotic pathways. It was mediated by oxidative stress and generation of ROS. The caspase-dependent apop-totic pathway was initiated by activation of caspase 4. Activation of caspase-4 and altholactone-induced apoptosis was significantly inhibited by pre-treatment of CRC cells with the antioxidant N-acetylcysteine. Altholactone was found to be less toxic to normal fibroblasts compared to 5-fluorouracil (5-FU) but not doxorubicin. Altholactone treatment was also reported to increase levels of iNOS and heat shock protein HSP70 in brain tissue. Serum biochemistry analysis of altholactone revealed an increase in the levels of alanine aminotransferase (ALT) [64]. Altholactone isolated from *Goniothalamus macrophyllus* was reported to induce apoptosis through Type II signaling pathway in cervical carcinoma HeLa cell.

Caspase 3 was activated by both extrinsic (DISC mediated) as well as intrinsic (mitochondrial-mediated) caspase cascade. Altholactone was reported to suppress oncogene Bcl2 and activate tumor suppressor gene p53 expression [66].

Altholactone was observed to induce growth inhibition of human bladder cancer T24 cells by apoptosis. Intracellular reactive oxygen species (ROS) triggered altholactone- induced apoptosis cell death in T24 cells. Altholactone was also found to promote the generation of ROS in T24 cells. Furthermore, apoptosis induced by altholactone was associated with decreased expression of Akt phosphorylation and activation of MAPK-p38. Akt regulates various cellular processes like cell proliferation and apoptosis; inhibitions of phosphorylated –Akt may induce for cancer cell apoptosis [67]. Altholactone modulates mitochondrial Bcl2 proteins and caspase-3 [58].

Recently, it was reported that altholactone exhibited cytotoxic effect against prostate cancer cells (DU145). The probable mechanism for cyto-toxicity of altholactone would be due to triggered cell cycle arrest in prostate cancer cell at S phase. Another mode of cell death induced by altholactone in prostate cancer cells would be due to elevated levels of ROS, followed by apoptotic cell death. The molecular mechanism of altholactone induced ROS-mediated apoptosis may be due to effect on transcriptional activities of various transcriptional factors like Nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3) and activator protein 1(AP1). NF-κB activates cell survival and proliferation signals, it's over-activation results in different types of cancer [58]. NF-κB is an activator of STAT3 signaling. Altholactone results in reduced expression NF-κB in prostate cancer cells. It also represses p65, TNFα and inhibited both constitutive and IL-6 induced transcriptional activity of STAT3. Altholactone treatment also results in down-regulation of STAT3 target genes such as Bcl-2 and survivin followed by up-regulation of pro-apoptotic Bax protein [57].

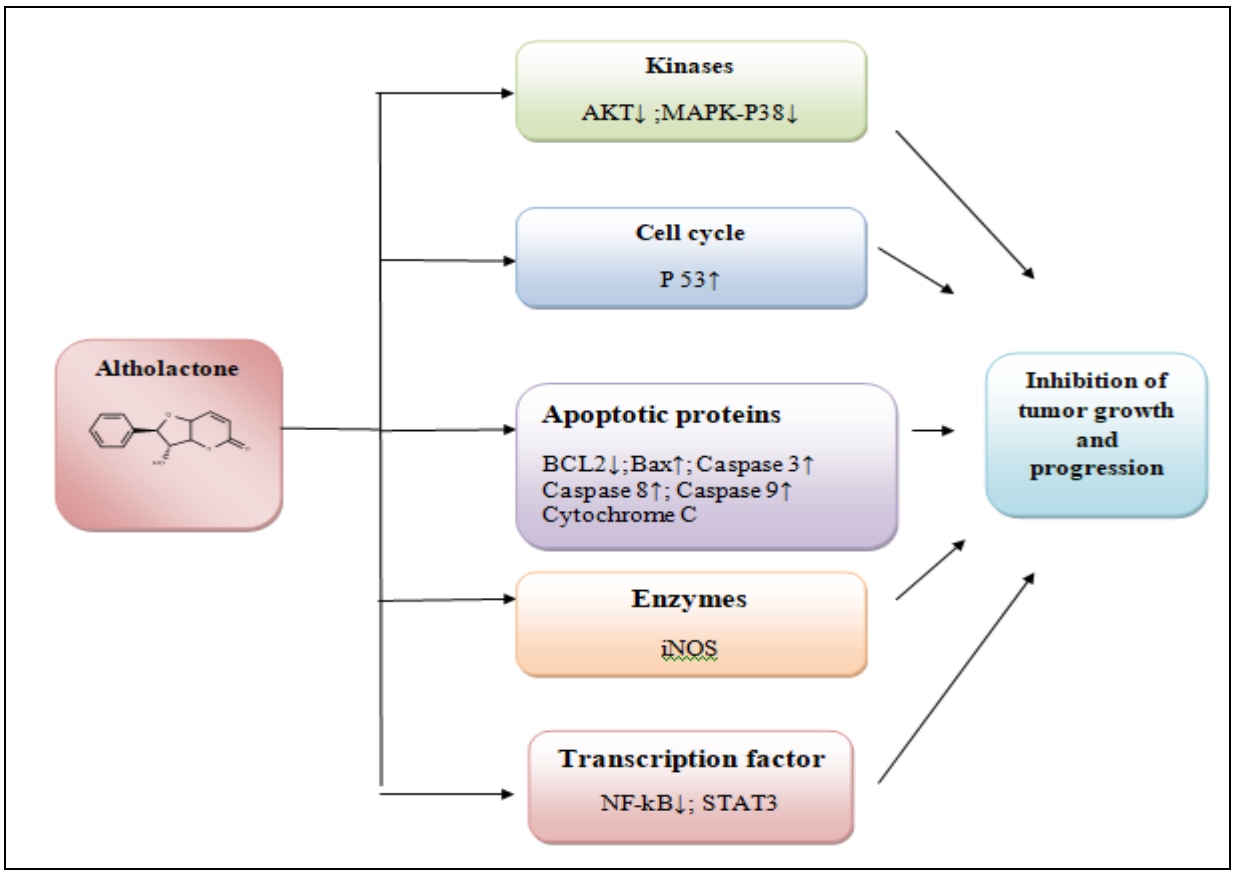

FIG. 2: ALTHOLACTONE TARGETS MULTIPLE CELL SIGNALING PATHWAYS. ALTHOLACTONE INHIBITS VARIOUS TARGETS, INCLUDING TRANSCRIPTION FACTORS, ENZYMES, GROWTH FACTORS, AND ITS RECEPTORS, KINASES, AND APOPTOTIC PROTEINS. NOTE: INOS, INDUCIBLE NITRIC OXIDE SYNTHASE; NF-κB, NUCLEAR FACTOR KAPPA B; BCL-2, B-CELL LYMPHOMA PROTEIN 2; BAX, BCL-2-ASSOCIATED X PROTEIN; P38MAPK, MITOGEN-ACTIVATED PROTEIN KINASES

Although the mode of action of altholactone is still not clearly understood. The probable mechanisms for cyctotoxicity of altholactone would be due to oxidative stress and mitochondrial abrogation and triggered cell cycle arrest [59, 62]. The current paradigms of apoptosis suggest that altholactone activate the caspases enzymatic cascade *via* a loss of mitochondrial transmembrane, which results in the release of mitochondrial cytochrome c [62]. Moreover, the protein kinase is involved in apoptosis by TNF-related apoptosis-inducing ligand (TRAIL). Altholactone induces apoptosis at TRAIL -BAX system level *via* protein kinase modulations [68].

3. SAR of Altholactone Derivatives with Anticancer Activity: The absolute configuration of natural isomer of altholactone was established by Gesson *et al*. [26] (+) altholactone (1) showed 3aR configuration and its enantiomer 3aS (-)-altholactone (2).

The natural isomer (+)-1 was found to be more active compared to the synthetically prepared (-)-1in cytotoxicity study against tumor cell line (L1210) [28]. Cytotoxicity exhibited by (+)-altho-lactone was in the range of methotrexate (Mtx) and 5-fluorouracil (5-FU). The relative orientation of phenyl ring at C-2 position played an important role in anti-tumor activity. 2R, 3R configuration proved essential for activity. (+)-altholactone was found to be the most active amongst the three stereo-congeners; (+)-7-epi-altholactone (7), (+)-8-epi-altholactone (13) and (+)-7,8-di-epi-altholactone (14). (+)-altholactone (1) exhibits weak cytotoxicity against oral epidermoid cancer (KB) cells, human colon cancer (HT-29), and mouse leukemia (L1210). (+)-Altholactone (1) and (+)-7-epi-altho-lactone (7) showed similar activity against colon cancer cells (HT-29); this indicates that the configuration at C7 does not influence cytotoxic activity. Analogs which possess S-configuration at C8 position were found to be five times more active than (+)-Altholactone (1) and (+)-7-epi-altholactone (7). These results suggest that the configuration of C8 is critical for the significant anti-tumor activity of furano-pyranone styryl lactone [34, 35].

Semi-synthetic derivatives of (+)-altholactone substituted with phenyl ring at ortho and para positions by an electron withdrawn substituent such as nitro (NO_2) exhibits antiproliferative activity. 11-nitroaltholactone (15), 9, 13-dinitro-altholactone (16) and 6, 7-dihydro-7-chloro-altholactone (17) show more cytotoxic activity against L1210 tumor cells compared to 6-Acetyl-3, 4-dihydroxy-6-methoxy-altholactone (18), triacetyl derivatives (19), methylenedioxy derivative (20), 7-methoxy derivatives of Altholactone (21). Introduction of trifluoromethyl (CF_3) group into the isoaltholactone at 7a position was attempted for enhanced anti-tumor activity [52]. Incorporation of strong electron-withdrawing groups in α, β unsaturated δ lactone ring renders it more electron-deficient, which may be reason for enhanced antiproliferative activity.

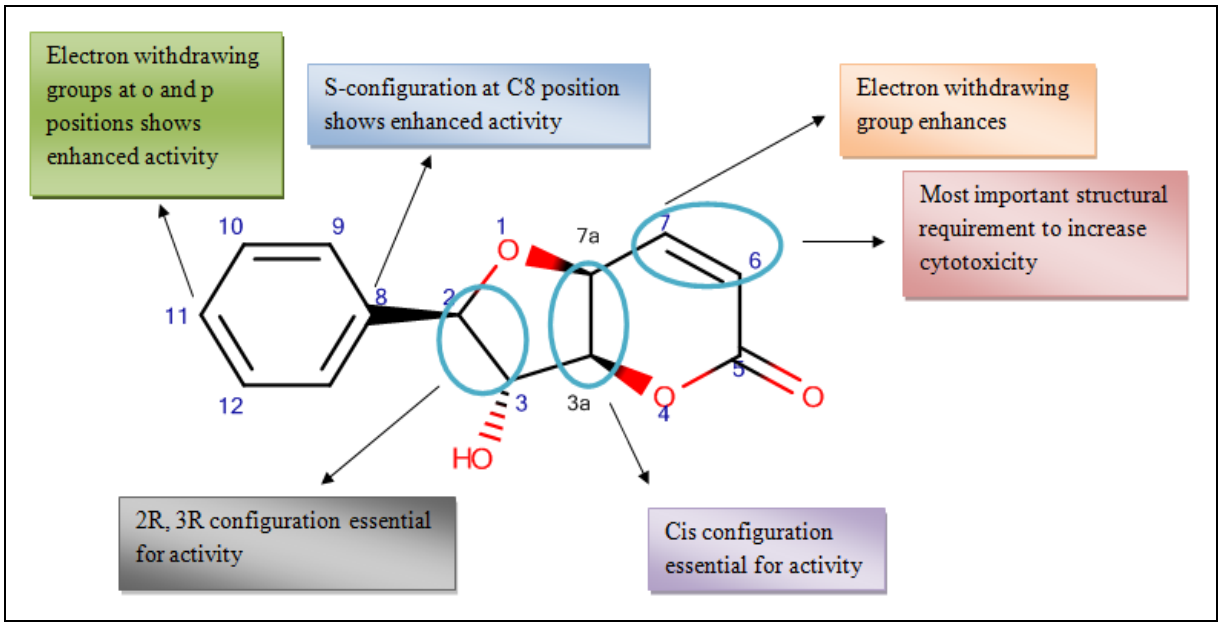

FIG. 3: STRUCTURE ACTIVITY RELATIONSHIP OF ALTHOLACTONE DERIVATIVES AS ANTICANCER AGENT

The presence of electron donating groups on the altholactone ring is observed to decrease cytotoxic activity. (+)- altholactone is most active in the furanopyrone series followed by (-)-altholactone and mono nitro derivative. Unsaturation at C6 and C7 position on the pyrone ring or chlorination at C7 position is most important structural requirement to increase the cytotoxicity [35]. Acetylation at C-3 hydroxy group in athlolactone increases inhibitory action against mitochondrial respiratory chain, which may account for cytotoxic and antitumor activity of the compound [59].

CONCLUDING REMARKS AND FUTURE PERSPECTIVE: This review summarizes isolation, synthesis, and anticancer activities of altholactone and its derivatives. Studies have shown that an altholactone analogue induces apoptosis of several types of the cancer cell. Based on SAR, it can be concluded that natural and synthesized altholactone derivatives could be regarded as lead molecules for the development of new cancer chemotherapeutic drugs. Thus, there is a wide scope for a synthetic chemist to synthesize substituted altholactone by alteration of the structure. Further investigations are required on substituted altholactone and its specific mechanisms to induce apoptosis in the cancer cell.

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