Cancer remains the most important causes of death all over the world as compared to other non-infectious diseases. According to cancer statistical report, about 14.1 million cancer cases and 8.2 million deaths due to cancer were reported in 2012 (Khan et al., 2016). Later, in 2018, GLOBOCAN estimated 18.1 million new cancer cases and 9.6 million deaths due to cancer (Ferlay et al., 2018). World Health Organization (WHO) predicted 17.5 million expected deaths at the end of 2050 due to cancer (Khan et al., 2016).

Among all, the second most common cancer in women is BC and one of the important causes of death (Kaur et al., 2019; Torres et al., 2019). Over 1.5 million
BC cases are diagnosed every year throughout the world. In 2018, about 2 million new BC cases were diagnosed (Zaidi and Dib, 2019).

ALAN increases the risk of BC due to suppression of MLT production (Stevens, 2005; Xiang et al., 2019). However, MLT production increases in the absence of light (Hill et al., 2009; Hill et al., 2015). MLT is mainly produced and secreted by the pineal gland (Korkmaz and Reiter, 2008; Li et al., 2017). In addition to pineal gland, it also synthesized by different organs like skin, gastrointestinal tract, retina, bone marrow, and lymphocytes (Hill et al., 2015; Li et al., 2017). Chemically, it is an indoleamine (N-acetyl-5-methoxytryptamine) and name (Mela-) is due to its effect on amphibians which blanch the melanophores and (-Tonin) because it is derived from serotonin (Basse and Arock, 2015). It is famous for ‘night hormone’ and supposed as ‘Jack of all trades (Haim and Zubidat, 2015). It plays an important role in regulating the immune system and sleep wake cycle. It also acts as an anti-oxidative, anti-aging, anti-inflammatory and anti-cancer agent. (Bondy and Campbell, 2018; Amin et al., 2019). The process of biosynthesis of MLT has been shown in Figure 1.

![Figure 1: Synthesis of MLT. MLT synthesis takes place in pineal gland. Pineal glands uptake tryptophan and converts into MLT through five enzymes catalyzed reactions. The diagram represents the sequential reactions and enzymes involved in biosynthesis of MLT. TPH: Tryptophan hydroxylase, 5-HTPD: 5-Hydroxytryptophan decarboxylase, SNAT: Serotonin N-acetyltransferase, HIOMT: hydroxyindole-O-methyl transferase.](image)

The production of MLT is controlled by the suprachiasmatic nucleus with the help of the pineal gland, which affects clock genes and reduces cancer (Blakeman et al., 2016; Zubidat and Haim, 2017; Giudice et al., 2018). During the day, the concentration of MLT reduces whereas its concentration increases at night. By exposure of ALAN, the normal action of MLT disrupts due to its less production (Sharma et al., 2010) which cause abnormal epigenetic changes that enhances the BC risk (Haim and Zubidat, 2015).

In 1942, C. H. Waddington first introduced the idea of epigenetic (Hasan et al., 2015). It controls genetic alternation without changes in sequence of DNA nucleotides (Kochan and Kovalchuk, 2015). Two major ALAN mediated epigenetic changes include methylation of DNA and acetylation of histone that are important to growth, development and progression (Lujambio and Esteller, 2008; Bondy and Campbell, 2018). These modifications are also increasing the chances of BC (Salavaty, 2015) by activation of oncogene and interruption of the role of particular TSGs (Lee and Muller, 2010). MLT regulates alternations in tumor cell. It performs anticancer activity by down-regulation of oncogenes and up regulation of TSGs. It also causes methylation and deacetylation of the oncogene (CYP19) that reduces BC. As a result of deacetylation, chromatin condenses and suppresses the binding of transcriptional factor which require for activation of oncogenes. Moreover, MLT also reduces BC by methylation of other oncogenes (Early Growth Receptor 3 and POU4F2/Brn-3b) and unmethylation of TS glypican- 3 (GPC3) (Lee et al., 2013). Epigenetic mechanism relates to inactivation of TSG and activation of oncogenes and these modifications affect genes expression (Haim and Zubidat, 2015).

Effect of ALAN at MLT secretions and estrogen production

ALAN influences the normal daily pattern because it contains light with different spectrum and wavelength (Keshet-Sitton et al., 2016). It decreases the concentration of MLT by the retinohypohalamic pineal region. Decrease in MLT results in increase level of estrogen, which also increases the risk of BC development (Blask et al., 2011; Dauchy et al., 2014; Bauer et al., 2013). It is thought, the main reason of BC risk is lifetime load with estrogen (Stevens, 2009; White et al., 2017).

Effect of ALAN on methylation of tumor suppressor genes

Among epigenetic alternations which are induced by ALAN, the most important is DNA methylation, and it is more common form of molecular fluctuations in human cancer. In DNA methylation, a methyl (–CH3) group shifts to the 5th carbon (5C) of cytosine from Sadenosyl- L-methionine (Fang et al., 2003; Mahmood and Rabbani, 2017; Pfeifer, 2018). Enzyme (known as DNA methyltransferase) involves the shifting of –CH3.
Figure 2: ALAN induced BC: MLT synthesis take place in pineal gland at night, however; ALAN reduced its production which results in abnormal epigenetic changes including DNA methylation and Histone acetylation. The promoter region is unmethylated and acetylated in normal tissue of TSG while it is methylated and deacetylated in cancer tissues. As a result, TSG become inactive and oncogenes become active leading to BC induction.

DNA Methylation is the most important mechanism in epigenetic alternations which is involved in regulation of genetic programming and enhances the progression of different types of cancers, including BC (Pouliot et al., 2015; Zubidat and Haim, 2017). These alterations occur only to a cytosine and guanosine sequence in the DNA, known as CpG dinucleotide. These regions are primarily present at the promoter and there is generally no methylation in normal cells (which permit the active gene transcription) while in cancer cells these CpG promoter region are methylated which results in silencing of various TSGs and pro-apoptotic genes (Basse and Arock, 2015; Wajed et al., 2001).

Several kinds of alternation in DNA methylation can take place in cancer, such as hypermethylation in gene-locus resulting in the inactivation of TSG, or hypomethylation of the distinctive genes and repeated sequences (Basse and Arock, 2015). Hypermethylation is the term used for more methylation while hypomethylation for less methylation (Ehrlich, 2002; Blask et al., 2003). These alternations act as a biomarker for identification as well as treatment of cancer (Radpour et al., 2009).

In case of BC, the expression of circadian genes is deregulated. Reports indicated hypermethylation on promoter of PER1, PER2, CRY1 and BMAL genes in BC (Kuo et al., 2009; Shanmugam et al., 2013; Salavaty, 2015). In long term shift workers, Cry2 (related to circadian genes) is hypermethylated on promoter region (Zhu et al., 2011; Steven and Zhu, 2015). Glypican-3 (GPC3), a tumor suppressor gene is aberrantly methylated in MCF-7 BC cell lines. Upon treatment of MCF-7 cells with 1nM MLT, significant increase in the expression of GPC3 genes.
gene was observed. The findings suggest that MLT could modulate methylation pattern of this tumor suppressor gene (Lee et al., 2013). In long term shift workers, the miR-34b promoter region is aberrantly methylated which enhanced the BC risk due to ALAN exposure (Liu et al., 2015). Report indicated the relationship between DNA methylation of TSG (BRCA1, BRCA2, TP53, CDKN2A) and night shift workers. It graphically showed the expression of methylation decreases from number of years in these TSG. Results indicted that in night shift workers, BRCA1 and TP53 are hypomethylated compared with non shift workers (Carugno et al., 2019). Hypomethylation of p53 and BRCA1 has been assumed to be induced to counterbalance defects in circadian cell cycle regulation and thus could indirectly increase the risk of cancer.

**Effect of ALAN on methylation of oncogenes**

Oncogenes included those genes that enhanced cell proliferation and survival (GRØNBÆK et al., 2007). Several types of genes in BC changed the level of their expression due to usual methylation. In cancer cells, the genome is globally hypomethylated or unmethylated that caused the instability of chromosome, and failure of genomic imprinting might result in the upregulation or more expression of proto-oncogenes (Jovanovic et al., 2010; Hasan et al., 2015). In several proto-oncogenes, the promoter region is hypomethylated or not methylated leading to uncontrolled cell proliferation, cancer progression and development of treatment resistance. The main epigenetic mechanism of BC is the activation of oncogenes due to inactivation of TSG that cause the cancer, including BC (Basse and Arock, 2015).

Oncogenes such as POU4F2 and ERG3 showed different methylation patterns and were up-regulated in BC cell lines. Treatment of BC cells with 1nM MLT, halted the growth of BC cells by down-regulating above said oncogenes via increased methylation. (Lee et al., 2013). CLOCK (related to circadian genes) is hypomethylated on the promoter region in shift workers. (Zhu et al., 2011; Steven and Zhu, 2015). Other independent studies conducted in CLOCK which showed slightly more methylation in BC cases compared with healthy control (Erdem et al., 2017). ALAN showed different results from the methylation of TSG and oncogenes. The results are shown in Table 1.

**Effect of ALAN on acetylation of tumor suppressor genes**

ALAN caused changes in usual acetylation pattern of TSG (Haim and Zubidat, 2015). The balance between histone acetylation and deacetylation is necessary for controlling the expression of genes. Histone acetylation is promoted by histone acetyl transferases enzyme (HAT) that is concerned with activation of gene transcription, whereas histone deacetylation or hypoacetylation is promoted by another enzyme called histone deacetylase (HDAC) which is associated with repression of gene transcription (Suzuki et al., 2009; Cohen et al., 2011; Li et al., 2013). Changed expression or gene mutations that encode histone deacetylation or hypoacetylation have been associated with induction of cancer while both these promote the abnormal transcription of leading genes and controlled the main functions of cells such as cell propagation, regulation of cell-cycle and apoptosis (Ropero and Esteller, 2007).

### Table 1: Effect of ALAN on methylation pattern of genes in BC.

<table>
<thead>
<tr>
<th>Gene/ Protein</th>
<th>MLT</th>
<th>Normal function</th>
<th>Methylation-Pattern</th>
<th>Effect</th>
<th>Activation/ Inhibition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 1</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Kuo et al., 2009</td>
</tr>
<tr>
<td>Per 2</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Kuo et al., 2009; Shanmugam et al., 2013</td>
</tr>
<tr>
<td>Cry1</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Kuo et al., 2009</td>
</tr>
<tr>
<td>BMAL1</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Kuo et al., 2009</td>
</tr>
<tr>
<td>EGR3</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Activation</td>
<td>Lee et al., 2013</td>
</tr>
<tr>
<td>POU4F2</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Activation</td>
<td>Lee et al., 2013</td>
</tr>
<tr>
<td>GPC3</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Lee et al., 2013</td>
</tr>
<tr>
<td>CLOCK</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Activation</td>
<td>Zhu et al., 2011; Steven and Zhu, 2015</td>
</tr>
<tr>
<td>CLOCK</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Activation</td>
<td>Erdem et al., 2017</td>
</tr>
<tr>
<td>Cry2</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Zhu et al., 2011; Stevens and Zhu, 2015</td>
</tr>
<tr>
<td>mir-34B</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↑</td>
<td>BC</td>
<td>Inhibition</td>
<td>Liu et al., 2015</td>
</tr>
<tr>
<td>BRCA1</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Inhibition</td>
<td>Carugno et al., 2019</td>
</tr>
<tr>
<td>BRCA2</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Inhibition</td>
<td>Carugno et al., 2019</td>
</tr>
<tr>
<td>CDKN2A (p16)</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Inhibition</td>
<td>Carugno et al., 2019</td>
</tr>
<tr>
<td>TP53</td>
<td>↓</td>
<td>TS</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Inhibition</td>
<td>Carugno et al., 2019</td>
</tr>
<tr>
<td>ESR1</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Activation</td>
<td>Carugno et al., 2019</td>
</tr>
<tr>
<td>ESR2</td>
<td>↓</td>
<td>Onco</td>
<td>-CH3↓</td>
<td>BC</td>
<td>Activation</td>
<td>Carugno et al., 2019</td>
</tr>
</tbody>
</table>

↓: Downregulation; ↑: Upregulation; TS: Tumor Suppressor; BC: Breast Cancer.

References: Li et al., 2013; Steven and Zhu, 2015; Cooper et al., 2019; Haim and Zubidat, 2015; Ropero and Esteller, 2007.
### Table 2: Effect of ALAN on acetylation pattern of genes in BC.

<table>
<thead>
<tr>
<th>Gene/Protein</th>
<th>MT</th>
<th>Normal Function</th>
<th>Acetylation/Deacetylation</th>
<th>Effect on BC</th>
<th>Activation/Inhibition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Proietti et al., 2014</td>
</tr>
<tr>
<td>CYP19</td>
<td>↓</td>
<td>Onco</td>
<td>Acetylation</td>
<td>BC</td>
<td>Activation</td>
<td>Korkmaz et al., 2009</td>
</tr>
<tr>
<td>ER</td>
<td>↓</td>
<td>Onco</td>
<td>Acetylation</td>
<td>BC</td>
<td>Activation</td>
<td>Saha and Corsi, 2007</td>
</tr>
<tr>
<td>c-MYC</td>
<td>↓</td>
<td>Onco</td>
<td>Acetylation</td>
<td>BC</td>
<td>Activation</td>
<td>Saha and Corsi, 2007</td>
</tr>
<tr>
<td>STAT3</td>
<td>↓</td>
<td>Onco</td>
<td>Acetylation</td>
<td>BC</td>
<td>Activation</td>
<td>Xiang et al., 2019</td>
</tr>
<tr>
<td>BRCA1</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Hill et al., 2009</td>
</tr>
<tr>
<td>BRCA2</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Hill et al., 2009</td>
</tr>
<tr>
<td>Per 1</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Hill et al., 2009</td>
</tr>
<tr>
<td>Per 2</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Hill et al., 2009</td>
</tr>
<tr>
<td>Ku-70</td>
<td>↓</td>
<td>TS</td>
<td>Deacetylation</td>
<td>BC</td>
<td>Inhibition</td>
<td>Hill et al., 2009</td>
</tr>
<tr>
<td>MMP</td>
<td>↓</td>
<td>Onco</td>
<td>Acetylation</td>
<td>BC</td>
<td>Activation</td>
<td>Bondy and Campbell, 2018</td>
</tr>
</tbody>
</table>

↓: Downregulation; ↑: Upregulation; TS: Tumor Suppressor; BC: Breast Cancer; Onco: Oncogene.

For alterations in chromatin, most important mechanism is the adaptation of histone acetylation and deacetylation. These adaptations cause epigenetic changes due to alternations in expression of gene and cell development which may affect carcinogenesis and propagation (Cui et al., 2018). In cancer, the functions of histone deacetyltransferase are not only limited to their involvement to histone deacetylation, but also played an important role in deacetylation of non-histone proteins. For instance, in vivo and in vitro study, histone deacetyltransferase 1 linked with the p53 (that is tumor suppressor) and deacetylated it (Ropero and Esteller, 2007).

MLT exhibited anticancer effects in BC. It decreased the MDM2 expression and increased acetylation of p53 in MCF-7 cell lines (Proietti et al., 2014). MLT via its receptor MT1, activated the RORα that controls the expression of SIRT1 (histone deacetylases) and BMAL/CLOCK. CLOCK (histone acetyltransferases) acetylated PER1/2 and other DNA repair genes BRCA1, BRCA2, P53 and Ku-70 which reduced the development of cancer due to acetylation activity. Hill et al., have explained, how BRCA1, BRCA2, P53, Ku70, PER1 and PER2 deacetylated and induced BC due to ALAN (Hill et al., 2009). The findings showed below recommend that ALAN causes more expression and abnormal recruitment of histone deacetyltransferases in promoter regions could be a regular event in cancer development and progression, resulting suppressed transcription of tumor-suppressor genes.

**Effect of ALAN on acetylation of oncogenes**

ALAN decreased the production of MLT and enhanced phosphorylation and acetylation of oncoprotein (such as STAT3) that over expressed in BC (Xiang et al., 2019). Hyperacetylation of Proto-oncogenes results in activation of proto-oncogenes while hypo-acetylation of tumor suppressors genes is frequently localized to promoter region causing the genes to be silenced (Audia and Campbell, 2016).

MLT has been reported to decrease the expression of CYP19 protein which is frequently overexpressed in BC cell lines. MLT exhibits oncostatic effects via deacetylation of CYP19 (Korkmaz et al., 2009). In addition, MLT induced hypoacetylation and decreased the activity of matrix metalloproteinase (MMP). Increased expression of MMPs have been noted in various types of tumor which mainly facilitate metastasis (Bondy and Campbell, 2018). CLOCK (histone acetyltransferases) promotes acetylation of different genes such as c- myc and ERα that induce BC due to acetylation (Saha and Corsi, 2007).

The collective findings published previously recommended that ALAN causes the more expression and abnormal recruitment of histone acetyltransferases in promoter regions which could be a regular event in cancer development and progression, resulting in activation of oncogenes. ALAN mediated acetylation of TSG and oncogenes has been shown in Table 2.

**Conflict of interests**

The authors declare there is no conflict of interest.

**References**


