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HDAC inhibitors and their potential towards cancer treatment

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Abstract: Histone deacetylases (HDACs) play a key role in chromatin structure modulation through deacetylation of histones leading to formation of highly compact DNA-histone complex. HDACs have been reported to be implicated in multiple types of cancers. Blocking the activities of histone deacetylases will help to overcome gene repression pressure and it would be possible to check the incessant growth of cells in tumour. Therefore the interest has been developed to design the HDAC inhibitors and their analogues and histone deacetylases are now considered as potential targets for their wide distribution in various forms of cancer. HDAC inhibitors display their role by regulating cyclin dependent kinases (cdK), inducing p21 and various preapoptotic genes like Bax, Bak, repressing the activities of growth factors like VEGF, repressing transcription factor HIF-1α facilitating arrest of cell cycle, modulating various signaling pathways like STAT signaling, AMPK signaling, inducing cell adhesion molecule E-cadherin.

Keywords: cyclin dependent kinase; histone deacetylase; carcinogenesis; HDAC inhibitor.

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1 Introduction

Histone deacetylases are family of proteins comprises four classes of HDACs. Class I histone decaetylases includes HDAC1, HDAC2, HDAC3 and HDAC8. Out of four members, HDAC1, HDAC2 and HDAC3 are distributed in the nucleus whereas HDAC8 is distributed in nucleus and cytoplasm. Class II histone deacetylases have been further classified into IIA and IIB. Class IIA includes four members HDAC4, HDAC5, HDAC7 and HDAC9. HDAC7 is distributed in nucleus, cytoplasm and mitochondria whereas HDAC9 is distributed in nucleus and cytoplasm. Class IIB includes two members HDAC6 and HDAC10. Both HDA6 and HDAC10 are distributed mostly in cytoplasm. Class III histone deacetylases includes sirtuins and Sir2. Sirtuins have been reported in mammals and it consists of 7 members: SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, and SIRT6 and SIRT7. Sir2 has been reported in yeast (Grozinger and Schreiber, 2002; Marmorstein, 2001; Grozinger et al., 1999; Shore, 2000). Class IV histone deacetylase includes lonely member HDAC11, which is distributed in nucleus as well as in cytoplasm. HDACs have been classified on the basis of the presence of cofactors as zinc dependent histone deacetylases and NADP dependent histone deacetylases. Zinc dependent histone deacetylasesincludes class I, II (A, B) and class IV. Class III is the representative of NADP dependent histone decaetylases. In this work we have considered class I and class II histone deacetyalses for discussion as they are mostly implicated and reported in cancer.

2 Histone deacetylase

Histone deacetylases are members of an ancient enzyme family found in plants, animals and fungi as well as archaebacteria and eubacteria (Leipe and Landsman, 1997). The activity of HDAC is directed at histones. Many of the histone deacetylases are partially cytoplasmic.HDA6, HDAC7, HDAC4, HDAC10 (Hubbert et al., 2002; Fischle et al., 2001; Zhao et al., 2001; Guardiola and Yao, 2002). Some members of these proteins target non-histone substrates, including tubulin and transcription factors and p53 (Hubbert et al., 2002; Ito et al., 2002; Yao et al., 2001). A total of 18 HDAC enzymes have been identified and classified on the basis of homology to yeast HDACs. Class I HDACS are related to the yeast RPD3 deacetylase and have close homology in their catalytic sites. Class II HDACs are related to yeast Hda1 (histone deacetylase) (Kahali

et al., 2012). HDAC were classified into two different phylogenetic classes class I and class II (Bjerling et al., 2002; Gao et al., 2002). Class II HDACs share domains with similarity to HDA1 another deacetylase found in yeast (Bjerling et al., 2002). A new member of HDAC were identified HDAC11 (Gao et al., 2002). Probability of involvement of class I and class I HDACs in cellular differentiation and developmental processes (Buggy et al., 2000; Galasinski et al., 2002).

3 HDAC activity

HDACs enzymes perform by removing the acetyl group from the histones comprising the nucleosome. Hypoacetylation brings about decrease in the space between the nucleosome and the DNA which is wrapped around it. Strength of wrapping of the DNA reduces its accessibility for transcription factors, and the consequence is transcription repression (Wade, 2001; Strahl and Allis, 2000; Yoshida et al., 2001). The catalytic domain of HDAC is formed by about 390 amino acid comprising a set of conserved residues. Removal of acetyl group takes place via charge-relay system facilitated by the presence of two adjacent histidine residues, two adjacent aspartic acid residues and one tyrosine residue (Buggy et al., 2000; Johnstone, 2002). One essential component of charge-relay system is the presence of Zn^{2+} ion which binds to the zinc binding site at the bottom of the pocket. All HDACs are considered to be equal sensitive to trichostatin A (Yoshida et al., 2001; Johnstone, 2002; Marmorstein, 2001).

3.1 Class I HDAC

HDAC1 and HDAC 2 are very similar enzymes with sequence identity about 78%. The catalytic domain constitutes the major part of the protein (Langer, 1976; Cress and Seto, 2000; Kao et al., 2000; Li et al., 2002). HDAC1 and HDAC 2 only show activity within a complex of proteins. These protein complexes comprise set of proteins necessary for modulating their deacetylase activity and for binding DNA with the proteins which assist the recruitment of HDACs to the promoter of genes to be regulated (Zhang et al., 1999). HDAC1 and HDAC2 form three protein complexes Sin3, nucleosome remodelling and deacetylating (NuRD) and CO-REST. Both Sin3 and NuRD includes a core complex comprising HDAC1, HDAC2, RbAp48 (which binds directly to histoneH4), and RbAp46. The core complex alone not capable of showing activity, it requires some co-factors (Galasinski et al., 2002; Zhang et al., 1999; Lelievre, 1979; Heinzel et al., 1997; Ashburner et al., 2001) HDAC1 and HDAC2 can bind directly to DNA binding protein Yin and Yang 1 (YY1), a cellular nuclear matrix nuclear protein), Rb binding protein-1 and Sp-1 (Yoshida et al., 2001; Kao et al., 2000; Li et al., 2002; Zhang et al., 1999; Lelievre, 1979; Heinzel et al., 1997; Ashburner et al., 2001; Ito et al., 2000; Taplick et al., 2001; Maser et al., 2001; Koipally et al., 1999; Wu et al., 2001; Nair et al., 2001). HDAC3 shares structural and functional similarities with other class I histone deacetylases. The complexes SMRT (silencing mediator for retinoic acid thyroid hormone receptors) and N-COR (nuclear receptor co-repressor) are factors required for HDAC3 activity. Both complexes function as co-repressor (Yang et al., 2002). HDAC8 is highly similar to HDAC3. It consists most of the catalytic domain in with NLS in the centre (Buggy et al., 2000; Yoshida et al., 2001; Bertos et al., 2001).

Class I HDACs performs various functions such as cell cycle regulation, cell differentiation, and tissue development. These enzymes display their activities by deacetylating histones and large number of non-histones and it regulate gene expression and several other cellular processes (Wang et al., 2012).

3.1.1 Class I HDACs as therapeutic targets

Most of the class I, II HDACs have been reported in pancreatic cancer cell lines. MGCD0103 is a class I sensitive HDAC inhibitor which captures growth by cell cycle arrest in G2/M phase and by p21 induction. MC1568 is a class II a selective HDAC inhibitor (Wang et al., 2012). Class I histone deacetylases HDAC1, HDAC2 and HDAC3 are highly expressed in renal cancer (Fritzsche et al., 2008). HDAC1, HDAC2 and HDAC3 have been reported to be differentially expressed in breast cancer (Müller et al., 2013). DNA damage-binding complex recruits HDAC1 to repress Bcl-2 transcription in human ovarian cancer cells (Zhao et al., 2013). Inhibition of class I HDACs in non-small cell lungs cancer by honokiol have been demonstrated (Singh et al., 2013). HDAC1 and HDAC2 are reported to be upregulated in colon cancer (Choi et al., 2001).

3.1.2 Class II HDAC:

Class II HDACs have been classified into IIa and IIb. HDACs HDAC4, HDAC5 and HDAC7 have been reported to interact with SMRT/N-CoR and the co-repressor BCoR (Bcl-6-interacting co-repressor) and CtBP. They also interact with myogenic transcription factor 2 (MEF2). Binding of MEF2 to IIa HDACs inhibits the function of MEF2. MEF2 plays a vital role as DNA binding transcription factor (Andreucci et al., 2002). HDAC6 differs from that of other members HDAC5 and HDAC7 because it contains two catalytic domains (Yoshida et al., 2001). HDAC6 performs as tubulin deacetylase which facilitates microtubule dependent cell motility (Hubbert et al., 2002). Member of HDAC, HDAC4 have been reported to repress p21 in cancer (Mottet et al., 2009). The role of HDAC7 has been studied in cancer cell proliferation (Zhu et al., 2011).

4 Molecular basis of cancer

Carcinogenesis is the consequence of genetic and epigenetic aberrations which brings about altered gene expression (Sharma et al., 2010). For long efforts have been made to reverse those effects which errored in causing cancer. Histone acetylation is one of the major epigenetic mechanisms involved in altering architecture of chromatin structure, and is modulated by the opposing activities of histone acetyl transferases and histone deacetylases. Histones whose lysine residues are heavily acetylated yields a more open chromatin structure, due to the repulsion of the negatively charged DNA strand by negatively charged acetylated lysine residues inducing transcriptional activation. Conversely histone deacetylation leads to gene repression, due to transcriptionally silent heterochromatin. Aberrant activity of histone deacetylases leading to repression of the genes which have been reported in various types cancers, including breast cancer. Hence, these enzymes are rational targets in cancer therapy to modulate gene expression, in particular genes involved in proliferation and differentiation. Novel histone deacetylase inhibitors have been developed, and preclinical and clinical data demonstrate their role in

treatment and prevention of breast cancer (You and Jones, 2012; Sawan and Herceg, 2010). We present here the rationale for targeting histone deacetylases in breast cancer and other various types of cancer which involve the implication of various members of histone deacetylases.

4.1 Cylin dependent kinases and cell cylce regulation

Regulation of cell cycle is important for survival. Cell cycle regulators possess two vital roles:

1 detecting and repairing DNA damage

2 preventing uncontrolled cell division.

There are two major classes of cell cycle regulatory molecules:

a cyclins which are regulatory subunits

b cyclin dependent kinases as catalytic subunit.

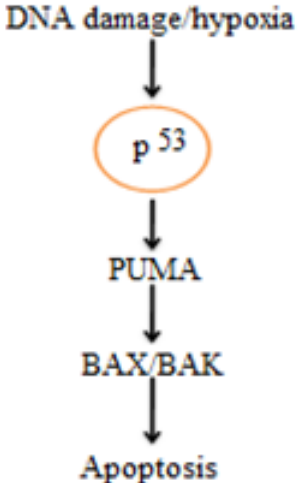
Cyclins are synthesiszed in the cell cycle and they possess none catalytic activity. Cyclin-dependent kinases are present within the cell and they come into action once they bind with cyclins. There are various types of cyclins: cyclin A, B, D and E. There are many types of CDKs. Cyclins when bound to cyclin-dependent kinases form maturation promoting factor which activates other proteins through phosphorylation. These phosphorylated proteins are responsible for vital events during cell cycle like microtubule formation and chromatin remodelling. Cyclins can be divided into four classes: G1/S cyclins, S cyclins, M cyclins and G1 cyclins. Cyclin-ddependent kinases are respsonsible for regulating transcription and mRNA processing. There are various types of cyclin-dependent kinases cdk1, cdk2, cdk3, cdk4.cdk11etc. CDK inhibitors are proteins that interact with cyclin-CDK complex to block kinase activity usually during G1 phase of the cell cycle or in response from signals from DNA damage (Sclafani, 1996; Morgan, 1995; Sherr, 1996; Matsushime et al., 1994). Overactivity of cyclin-ddependent kinases have been reported in cancer. Inhibition of cyclin dependent kinases may cause both cell cycle arrest and apoptosis. As histone decaetylase inhibitors are known to downregulate cyclins and cyclin-dependent kinases. It would be crucial for cell cycle regulation (Sharma et al., 2008; Shapiro, 2006).

4.2 Bax and Bak in apoptosis

Cellular proteins like BID, BIM and PUMA plays an important role in activating Bax and Bak (Ren et al., 2010).

Histone deacetyalse inhibitors have been reported in activating Bax and Bak as well as PUMA. PUMA mediates p53 dependent and independent apoptosis. PUMA transcription is activated to induce apoptosis via mitochondria through a Bax/Bak dependent manner. p53 activates PUMA to induce apoptosis following DNA damage, hypoxia. Histone decaetylase inhibitors down regulates hypoxia-inducible factor facilitating apoptosis (Figure 1).

Figure 1 Apoptosis induced by BAX/BAK (see online version for colours)



4.3 p21, p27 in cell cycle regulation

p21, p27 are known as cyclin dependent kinase inhibitor that bind and inhibit cyclin-CDK complex, thereby inducing cell cycle arrest. Following DNA damage p21, p27 are stimulated to bind to cyclin-CDK complex and halts the progress of the cell cycle (Figures 2 and 3). Histone deacetyalse inhibitors are known to upregualte p21 and p27 to regulate the cell cycle (Ren et al., 2010).

Figure 2 Cell cycle regulation by cyclin/cyclin-dependent kinase (see online version for colours)

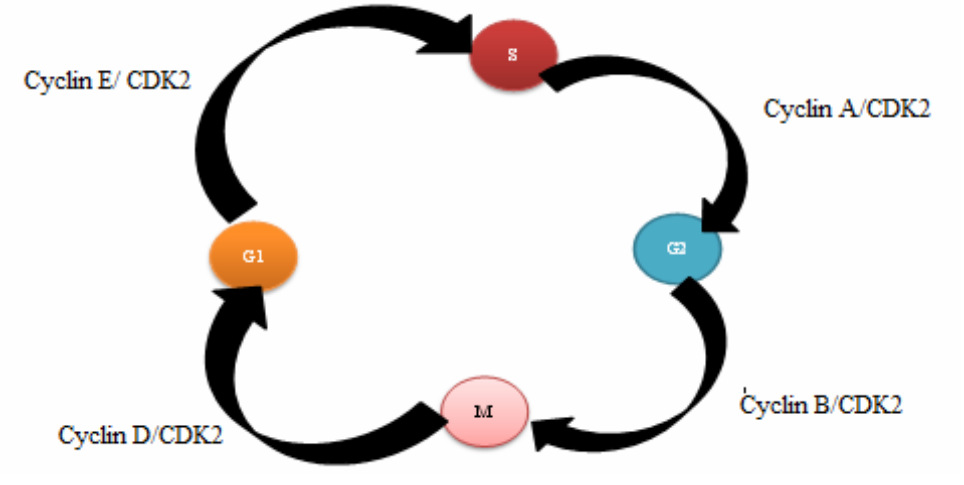
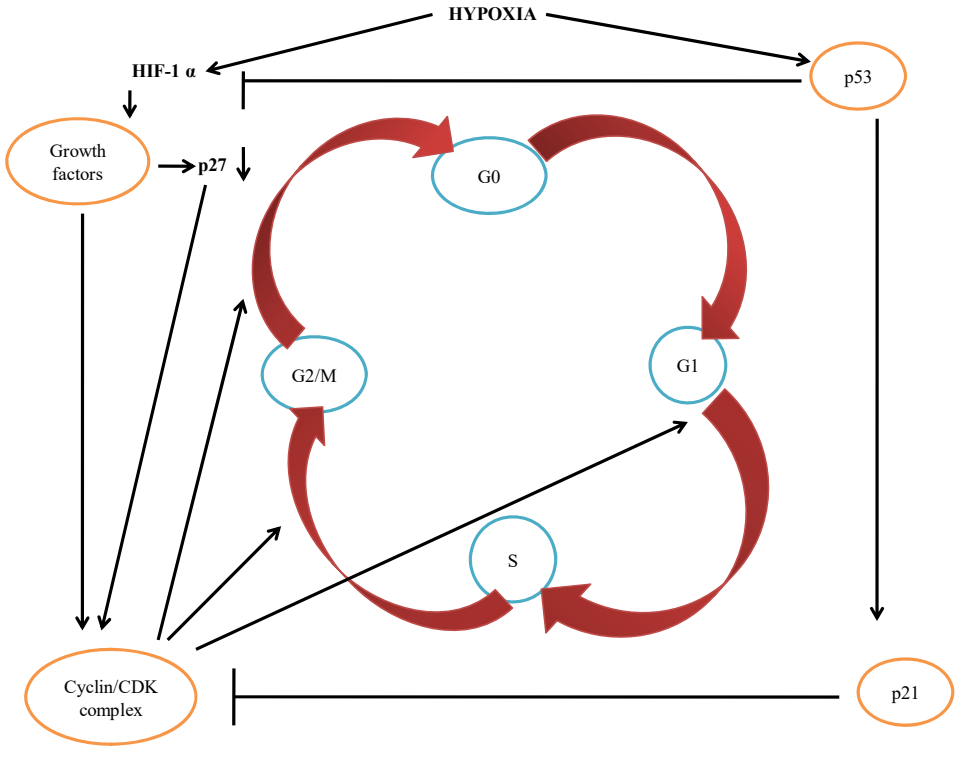


Figure 3 Regulation by cell-cycle by p21, p27 (see online version for colours)



5 HDAC inhibitors classification

Histone deacetylase inhibitors represent class of compounds which do away with the functions of histone deacetylases. It is shown in Table 1. Histone deacetylase inhibitors have been clinically tried in treatments of various disorders such as cancer of multiple types like breast cancer, prostate cancer, ovarian cancer, lungs cancer (Abbas and Gupta, 2008; Qian et al., 2006; Chen et al., 2010). HDAC Inhibitors and their targeted histone deacetylase classes are shown in Table 2. HDAC inhibitors have been classified to different classes:

1 hydroxamic acid-based inhibitors referred to as hydroxamates

2 cyclic tetrapeptides and depsipeptides

3 benzamides

4 electrophilic ketones

5 small aliphatic fatty acid compounds.

Table 1 Classification of HDAC

CLASS		*HDAC members*	*Co-factor*
CLASS I		HDAC 1, HDAC2, HDAC3, HDAC8	Zn
CLASS II	IIa	HDAC4, HDAC5, HDAC7, HDAC9	Zn
	IIb	HDAC6, HDAC10	Zn
CLASS III		SIRT(1-7) Sir2	NADP
CLASS IV		HDAC 11	Zn

Table 2 HDAC Inhibitors and their targeted histone deacetylase classes

	HDAC INHIBITOR	*CLASS SP*	*N/S*	*PMID*
1	DILINOLYLMETHANE (DIM)	HDAC2	N	22800507
2	APHA	CLASS I	S	18568166
3	APIGENIN	HDAC1, HDAC3	N	22006862
4	LARGAZOLE$^{\beta}$	CLASS I	N	18507379
5	HC-TOXINS$^{©}$	HDAC11	N	16839576
6	CHALCONE$^{\beta}$	HDAC	N	22710558
7	BIS (4-hydroxybenzyl sulphide)	HDAC	N	17851433
8	HYDROXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
9	HYDROXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
10	METHOXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
11	DIMETHOXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
12	HYDROXYCHALCO	CLASS I	N	22710558
13	DIMETHOXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
14	ISOLIQUIRITIGENIN$^{\Omega}$	CLASS I	N	22710558
15	CALOMELANONE$^{\Omega}$	CLASS I	N	22710558
16	BUTEIN$^{\Omega}$	CLASS I	N	22710558
17	FLAVOKAWQAIN C$^{\Omega}$	CLASS I	N	22710558
18	GYMNOGRAMMENE$^{\Omega}$	CLASS I	N	22710558
19	HOMOBUTEIN$^{\Omega}$	CLASS I	N	22710558
20	DIMETHOXY-2'-HYDROXYCHALCONE$^{\Omega}$	CLASS I	N	22710558
21	FLAVOKAWAIN A$^{\Omega}$	CLASS I	N	22710558
22	FLAVOKAWAIN B$^{\Omega}$	CLASS I	N	22710558
23	ERIOLDICTYOLCHALCONE$^{\Omega}$	CLASS I	N	22710558
24	PHLORETIN$^{\Omega}$	CLASS I	N	22710558
25	PHLORIDZIN$^{\Omega}$	CLASS I	N	22710558
26	ALLYL MERCAPTAN (AM)$^{\epsilon}$	HDAC	N	18628250
27	SULFORAPHANE$^{\epsilon}$	HDAC	N	19812222
28	ALLYLISOTHIOCYANATE$^{\epsilon}$	HDAC	N	19197985
29	BENZYLISOTHIOCYANATE$^{\epsilon}$	HDAC	N	20484017

Note: N – natural, S – Synthetic.

Table 2 HDAC inhibitors and their targeted histone deacetylase classes (continued)

	HDAC INHIBITOR	*CLASS SP*	*N/S*	*PMID*
30	PHENYLHEXYLISOTHIOCYANATE€	HDAC	N	16596246
31	PEITC €	HDAC	N	22247744
32	AN9 (PIVANEX)£	HDAC	S	16373710
33	BELINOSTAT (PXD101)α	CLASS I, II	S	12939461
34	CI-994ψ	HDAC1, 2	S	12700284
35	DACINOSTAT (NVPLAQ824)α	CLASS I, II, III and IV	S	12816865
36	SB939 (PRACINOSTAT)	CLASS I, II and IV	S	21285985
37	MS-275 (ETINOSTAT)ψ	CLASS I	S	17383217
38	GIVINOSTAT (ITF2357)α	CLASS I, II, III and IV	S	19633847
39	MOCETINOSTAT (MGCD0103)ψ	CLASS I	S	21317455
40	PANOBINOSTAT (LBH589)α	CLASS I, II	S	19344997
41	ROMIDEPSIN (DESPIPEPTIDE)β	CLASS I	N	12208741
42	VALPROIC ACID£	CLASSI, IIa	S	11742974
43	CHAP31α	HDAC1	S	11389076
44	AZUMAMIDE E©	HDAC1, HDAC2 and HDAC3	N	17311384
45	TUBACINα	CLASS II	S	12677000
46	SK-7041π	HDAC1 and HDAC2	S	15297431
47	SK-7068π	HDAC1 and HDAC2	S	15297431
48	PYROXAMIDEπ	CLASS I	S	11309347
49	DEPUDECIN	CLASS I	N	9520369
50	ACY-1215 (Rocilinostat)	CLASS I	S	22262760
51	4SC-202	CLASS I	S	N/A
52	PARTHENOLIDE	HDAC1	N	17656318
53	THIALANDEPSIN	CLASS I	N	22531354
54	DROXINOSTAT	HDAC3, 6 and 8	S	20053768

Note: N – natural, S – Synthetic.

Classification of HDAC inhibitors:

HYDROXAMIC ACID	α
CYCLIC PEPTIDES	β
BENZAMIDES	ψ
FATTY ACIDS	£
AROMATIC KETONES	Ω
THIOL	€
CYCLICTETRAPEPTIDE	©

SYMMETRIC DISULPHIDE	☋
MERCAPTOKETONE	μ
HYBRID INHIBITORS	π

5.1 Method of control of breast cancer by these inhibitors

Hyperacetylation is the most common phenomenon of HDACs inhibitors in regulating growth and differentiation of cell. Histone deacetylase inhibitors are involved in regulating cell cycle. These inhibitors capture cell cycle progression at various phases such as G1 phase, G2 phase and S phase. Many of these inhibitors induce p21 which is cyclin dependent kinase inhibitor1. p21 binds to and inhibits the activity of cyclin-dependent kinase-1, 2, 4/6. By doing so, p21 regulates cell cycle progression at G1 and S phase. Induction of expression of p21 by these inhibitors could be p53 dependent or independent mechanism. p21 can promote cellular differentiation by arresting growth of the cell. p21 mediated cell cycle regulation and its deregulation and therapeutic targets in cancer have been reported (Vermeulen et al., 2003). There are inhibitors which modulate HIF-1α. HIF-1α referred to as hypoxia inducible factor-1-alpha is a key regulator responsible for promoting genes which assist in survival of cells from hypoxia (low oxygen concentration) (Wang et al., 1995). The histone decaetylase inhibitors bring about downregulation of HIF-1α. Histone deacetylase inhibitors have been reported to downregulate the expression of vascular endothelial growth factor (VEGF) which is a growth factor induces vascularisation of blood capillaries that is angiogenesis. VEGF is a key mediator of angiogenesis in cancer (Carmeliet, 2005). Angiogenesis is essential for cancer progression and growth. Vasucularisation enriches with nutrients and oxygen. Under the influence of VEGF tumours are getting adequate amount of nutrients which facilitates their growth. The inhibitors promote expression of tumour suppression p53. p53 is one of the vital target of multiple histone deacetylases which through chromatin deacetylation represses the p53 expression. Histone decacetylase inhibitors relieve from chromatin condensation by hyperacetylatin histones and induce expression of p53. Some of the histone decaetylase inhibitors induce the expression of E-cadherin. E-cadherin is a calcium-dependent cell-cell adhesion molecule with vital role in epithelial cell behaviour, tissue formation and stunting growth of cancer (Van Roy and Berx, 2008). Histone deacetylases are implicated in epigenetic silencing of E-cadherin thereby promotes tumour development. Negative regulation of oestrogen receptor has been implicated in triple negative breast cancer, which is responsible for poor prognosis of breast cancer. Oestrogen is the ligand for oestrogen receptor-alpha. The ligand-ER complex functions as a transcription factor in multiple molecular pathways. The expression level of ER is vital in determining cellular growth (Pinzone et al., 2004). Histone deacetylase inhibitors contributes to hypercaetylation of histone and induce reexpression of oestrogen receptor. ER has been vital target of HDAC inhibitor in treating breast cancer. There are some HDAC inhibitors which regulates breast cancer through ER dependent ER independent pathways. HDAC inhibitors like chalcones downregulates the expression of cellular growth promoting proteins such as Cyclin B1, Cyclin A and Cdc2. Chalcones also mediate Fas/Fasl mediated apoptosis. Fas mediated apoptosis plays important role in arresting growth of the cells (Chu et al., 1995). Human endothelial receptor 2 (HER2) is implicated in breast cancer and it is responsible for poor prognosis of breast cancer.

Histone deacetylase inhibitor brings about repression of HER2. Signal transducer and activator of transcription have been reported in regulating expression of gene. STAT3 after being phosphorylated repress the expression of various genes.

Histone deacetylase inhibitors targets STAT3 and regulate cellular growth through activating/deactivating STAT3. STAT3 is phosphorylated at tyrosine through interleukin-6/glycoprotein 130/janus kinase pathways in breast cancer (Berishaj et al., 2007). HDAC inhibitors inhibit STAT3 mediated transcriptional regulation and control breast cancer growth. HDAC inhibitors promote expression of proapoptotic proteins such as Bax and Bak. Histone decaetylase inhibitors promote expression of Bcl2, Bcl-X, as these are anti-apoptiotic proteins. The inhibitors also reduce phosphorylation of Akt and S6K1 kinases. Akt is a proto-oncogene which gets activated after phopsphorylation and avails oncogenic properties (Bellacosa et al., 1998). Histone decaetylase inhibitors target Akt and prevent it from being active. Like Akt, S6K gets phosphorylated for activation. S6 kinase is an effector of TORC1. TORC1 promotes anabolic and inhibits catabolic cellular functions. TORC1 phosphorylates S6K1 and controls fundamental cellular process (Magnuson et al., 2012).

5.2 Specific HDAC inhibitors and their mechanism of regulating breast cancer

- *Panobinostat:* Panobinostat is a cinnamic hydroxamic acid analogue with promising antineoplastic activity. It selectively inhibits histone deacetylase inducing hyperacetylation of core histone proteins resulting in cell cycle arrest and apoptosis. These inhibitors also modulate the expression of hypoxia-inducible factor-1alpha (HIF-1a) and vascular endothelial growth factor (VEGF) as a consequence impairing endothelial cell chemotaxis andinvasion (Lemoine et al., 2012).Targeting triple negative breast cancer cells with the histone deacetylase inhibitor panobinostat (Tate et al., 2012). Panobinostat enhances histone acetylation, decreased cell proliferation and survival and blocks cell cycle progression with decrease in S phase. Panobinostat up-regulates CDH1 protein. Biochemical studies show that panobinostat induces H3 (Lys9) and H4 (Lys8) acetylation in triple negative breast cancer cell lines at 100, 200nM. It decreases TNBC cell proliferation and viability. Apoptosis is reported to be induced by panobinostat.
- *Vorinostat:* a phase II study of the histone decaetylase inhibitor have been studied in combination with vorinostat in combination with tamoxifen for the treatment of the patients with hormone therapy resistant breast cancer. Vorinostat is also known as suberanilohydroxamic acid (SAHA) is a member of larger class of compounds that inhibits histone decaetylase. It was the first HDAC inhibitor approved by FDA for the treatment of cancer. Vorinostat has been tested in patients suffering from metastatic breast cancer. Despite of results of disease stabilisation in 30% of the tested patients no clinical response were achieved (Luu et al., 2008). It has been reported that HDAC inhibitors are capable of resensitising tamoxifen resistant cells to hormone therapy and it has been hypothesised to check hormone therapy resistance (Yang et al., 2001; Zhou et al., 2007; Thomas et al., 2011). These studies reveal that HDAC inhibitors redirects tamoxifen treated breast cancer cells into apoptosis. From studies it is evidenced that inclusion of HDAC inhibitors vorinostat to tamoxifen results in prolonged disease stabilisation. It causes tumour regression and prolonged disease stabilisation (Munster et al., 2011). Vorinostat is also called as

MS344, suppresses MCF-7 breast cancer cell proliferation (Yeung et al., 2012). M344 is a potent suppressor of breast cancer. M344 caused significant concentration dependent decreases in MCF-7 cell proliferation. On treatment of MCF-7 cells with M344 there was increase in p21 mRNA expression. On the other hand it causes decrement in p53 expression whereas increase in puma and bax mRNA level has been revealed. These findings suggest provide evidence that M344 inhibits MCF-7 cell growth independent of p53 (Alao et al., 2006).

- *Trichostatin A:* trichostatin A is an antifungal antibiotic which selectively inhibits class I and class II HDACs. It inhibits cell cycle in the beginning of the growth phase. It has potential as anticancer drugs. TSA inhibits HDACs 1, 3, 4, 6 and 10 with IC50 values about 20nM. Histone deacetylase inhibitor TSA induces ubiquitin dependent cyclin D1 degradation in MCF-7 breast cancer cells. Cyclin D1 has been reported to have an important role in breast cancer cell proliferation. It is an important regulator of G1-S phase cell cycle transition. Studies show that TSA induces cyclin D1 26s proteasomal degradation (Rhodes et al., 2012). Trichostatin A alters microRNA expression profiles in apoptosis resistant breast cancer cells. It has been demonstrated that TSA suppresses in vitro clonogenic survival of the apoptotically resistant MCF-7TNR cells (Vigushin et al., 2001). Potent antitumour activity of TSA has been studied against breast cancer in vivo (García-Morales and Castro-Galache, 2002). Trichostatin A has been studied to be effective in various drug resistant tumour cell lines. It has been reported to reduce cell survival and promoting apoptosis in different drug resistant cells (Margueron et al., 2004). Histone deacetyalse inhibition and oestrogen receptor alpha levels modulate the transcriptional activity of partial antioestrogens. In several breast cancer cell lines trichostatin TSA, potent HDAC inhibitors strongly decrease ER alpha expression in a dose dependent manner (Margueron et al., 2004).
- *Etinostat* is a benzamide histone deacetylase inhibitor. It inhibits class I histone deacetylases HDAC1 and HDAC3. It causes epithelial to mesenchymal transition of breast cancer cells reversing the repression of E-cadherin. Epigenetic silencing of E-cadherin is revealed in metastatic cell lines and invasive breast cancers. Etinostat induces the expression of E-cadherin (Shah et al., 2014).
- *DIM:* Diindolylmethane is a natural compound found in cruciferous vegetables. It's a promising agent for the prevention of oestrogen sensitive cancers. Both DIM and oestrogen affect transcription of genes by binding receptors such as aryl hydrocarbon receptor (AhR) or oestrogen receptor. DIM can directly associates with oestrogen receptor, recruiting co-activators that bind to oestrogen responsive promoters and induce transcription (Mulvey et al., 2007).
- *Sodium phenylbutyrate:* it is a histone decaetylase inhibitor and chemical chaperone being used as anticancer agent. Phenylbutyrate inhibits the invasive properties of prostate and breast cancer cell lines. It can induce cell differentiation and apoptosis in a number of cancer cell types. The inhibitory activity of phenylbutyrate on metastatic invasion is not readily reversible. Studies have been done which reports prolonged treatments with phenylbutyrate may induce apoptosis directly in cancer cells (Dyer et al., 2002).

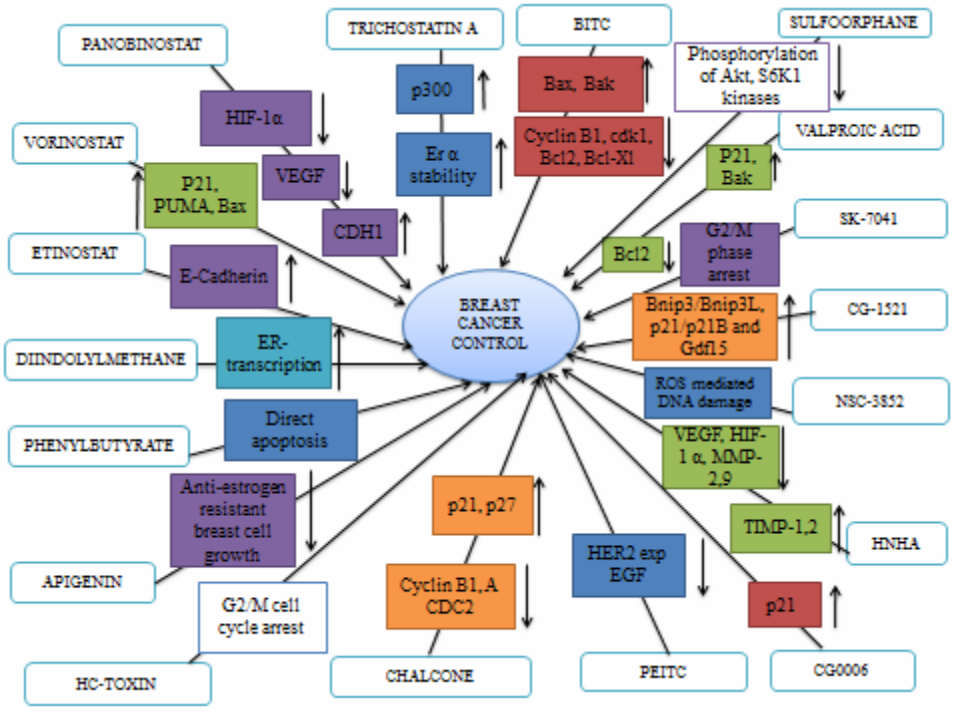
- *Apigenin:* apigenin is a natural product belonging to the flavone class that is the aglycome of several naturally occurring glycosides. Apigenin inhibits antioestrogen-resistant breast cancer cell growth through oestrogen receptor alpha dependent and oestrogen receptor –alpha independent mechanism. Breast cancer resistant to the antioestrogens tamoxifen induces alterations in both oestrogen dependent and oestrogen independent signaling pathways. In order to inhibits proliferation of anti-oestrogen resistant breast cancer cells it is required to block both the pathways. The studies reveal that apigenin can function as oestrogen as well as antioestrogen. It holds potential for being an effective compounds for the treatment of breast cancer by targeting dual pathways: ERα dependent and ERα independent pathways (protein kinases pathways) (Long et al., 2008).
- *HC-TOXIN:* it is a cyclic tetrapeptide is a virulent determinant for the plant pathogenic fungus. It's a widespread class of secondary metabolites. It is a potent inhibitor of histone decaetylase activity. It has been reported that HC-toxin exhibits capability of antiproliferative action and cell cycle arrest at G2/M in T47D human breast cancer cells. Potency of HC-toxin has been reported in oestrogen receptor positive human breast cancer cell lines T47D (Joung et al., 2004).
- *Chalcone:* Chalcone is an aromatic ketone and enone that forms central core of variety of important biological compounds collectively called as chalcones. Chalcones have been reported to inhibit the proliferation of human breast cancer cells by switching off cell cycle progression and triggering apoptosis. In the studies made against MCF-7 and MDA-MB-231 cell lines using chalcones, the result shown that proliferation of these cell lines were inhibited by chalcones. Chalcone reduces the expression of multiple proteins such as cyclin B1, cyclin A and Cdc2 proteins. On the other hand chalcone increases the expression of p21, p27 in p53 independent way (Gupta and Srivastava, 2012). Fas/Fasl mediated apoptosis by chalcones have been reported against breast cancer cell line MCF-7 and MDA-MAB-231 cells (Hsu et al., 2006). Chalcone activated apoptosis through mitochondrial pathways have been confirmed. Phenyl isothiocyanate is naturally occurring isothiocyanate reported in cruciferous vegetables. Antitumour activity of phenyl isothiocyanate in HER2-positive breast cancer models has been demonstrated. HER2 is an oncogene, its expression reasoned for poor prognosis in about 30% of breast cancer patients. Studies reveal that uses of phenyl isothiocyanate against breast cancer cells such as MDA-MB-231 and MCF-7, reduced the viability of the cells with IC50 8μM and 14μM respectively (Gupta and Srivastava, 2012). Breast cancer cells after being subjected to phenyl isothiocyanate, it was evidenced that there is reduction in expression of HER2, epidermal growth factor receptor and phosphorylation of STAT3. Benzyl isothiocyanate, a component of dietary cruciferous vegetables has antioxidant and anticancer properties. It is one of the members of chalcones. Benzyl isothiocyanate induced apoptosis in human breast cancer cells is triggered by reactive oxygen species and regulated by Bax and Bak. This compound is reported to inhibit the growth of cultured human breast cancer cells MB-231 and MCF-7, by capturing G2/M phase of cell cycle. BITC associated inhibition of cell cycle leads to decrease in protein levels of cyclin B1, cyclin-dependent kinase 1 and cell division cycle 25C. It induces proapoptotic proteins Bax and Bak and brings about upregulation of antiapoptotic proteins BCL-2 and Bcl-Xl (Xiao et al., 2006).

- *Sulfoorphane:* sulfoorphane is a molecule with the isothiocyanate group of organosulfur compounds. It exhibits anticancer properties in experimental models. This compound is an inducer of protective enzymes that provide defence against cancer causing chemicals. It has been reported that sulfoorphane can inhibits human breast cancer cells (Johnston, 2004). Sulfoorphane is a potent inhibitor of breast cancer cells. In MDA-MB-231, MCF-7, SKBR-3, MDA-MB-468 cancer cells sulfoorphane decreased phosphorylation of Akt and S6K1 kinases (Pawlik et al., 2013).
- *Valproic acid:* valproic acid is an acidic chemical compound has found clinical uses as an anticonvulsant compound and mood stabilising drug. It has been demonstrated that valproic acid serves as a selective antiproliferative agent in oestrogen sensitive breast cancer cells. In MCF-7 cells valproic acid causes apoptosis, downregualtion of Bcl-2 and upregulation of proapoptotic protein Bak expression (Fortunati et al., 2008). In oestrogen sensitive cell lines in decreases cell survival, promotes p21 expression. It induces G1 cell cycle arrest in ZR-75-1 cell line. It induces p21 expression in MCF-7 as well as in ZR-75-1 cells.
- *SK-7041:* SK-7041 is a novel hybrid synthetic histone deacetylase inhibitor. It was synthesised from part of hydroxamic acid of trichostatin A (TSA) and pyridyl ring of MS-275. It has been demonstrated that SK-7041 induces histone hyperacetylation and comparatively more potent cytotoxicity in breast cancer cells (Lee et al., 2006). This compound induces cell cycle arrest in breast cancer cell line MDA-MB-231. It induces apoptotic cell death by capturing G2/M phase of cell cycle. The anticancerous activity of SK-7041 on lungs and breast cancer cells has been so far tested in two cancer cell lines A549 and SK-BR-3 (Park et al., 2004; Kim et al., 2003).
- *CG-1521:* pan HDAC inhibitor.CG-1521 is a hydroxamic acid-based inhibitor. Studies conducted on apoptotic effect of CG-1521 reveals that it shows apoptotic activity comparatively earlier and rapidly another hydroxamic-based inhibitor SAHA. CG-1521 induces the expression of several p53 target genes associated with apoptosis such as Bnip3/Bnip3L, p21/p21B and Gdf15. The apoptotic effect of the inhibitor has been tested on MCF-7 human breast cancer cells. CG-1521 induces apoptosis by arresting G0/G1 arrest (Knutson et al., 2012).
- *NSC3852* is histone deacetylase inhibitor. It posseses cell differentiation and antiproliferative activity in human breast cancer cells. This compound induces free radical generation in MCF-7 breast cancer cells. It has been reported that NSC3852 causes ROS and oxidative stress mediated DNA damage and apoptosis in MCF-7 cancer cells. It also helps to generate hypophosphorylated Rb (retinoblastoma). Hypophosphyralated Rb is active tumour suppressor state (Martirosyan et al., 2006).
- *HNHA* is a histone deacetylase inhibitor. It's a synthetic molecule and it shows better pharmacological properties. HNHA inhibits the cell cycle at G1/S phase through p21 induction. HNHA treated breast cancer cells shown decrease in vasucular endothelial growth factor (VEGF) and hypoxia inducible factor 1 alpha (HIF-1α). Studies have been done which confirm HNHA as anti-tumour agent in breast cancer cells. It has anti-angiogenic activity and inhibitory activity against histone decaetylases (Park et al., 2011). It has been reported that HANHA brings about elevation of TIMP-1,

TIMP-2 and downregulation of MMP-2, MMP-9.BML-210 is a histone deacetylase inhibitor. It has been reported that BML-210 either alone or in association with retinoic acid induces increase in level of p21. It also causes elevation in anti-apoptotic protein Bcl-2 and phosphorylated p38 MAP kinase.

- *CG0006* is a novel histone deacetylase inhibitor. It is described as hydroxamate-based pan histone deacetylase inhibitor. Its activity has been reported in suppression of the growth of human cancer cells. Studies have been conducted which reveals that CG0006 increases histone H3 and H4 acetylation, upregulation of p21 protein capturing cell cycle. In both the cell types MCF7 and MDA-MB-231, CG0006 decreases the level of oestrogen signalling proteins ERα and cyclin D1. It inhibits histone deacetylase6 and also increases Hsp90 and alpha tubulin acetylation. This inhibitor inhibits breast cancer cells by dual mechanism through histone acetylation dependent pathway and non-epigenetic pathway which disrupts chaperone function. It induces G2/M-phase accumulation in ER+VE MCF7 cells and G1, G2/M phase accumulation in ER-ve MDA-MB-231 cells (Kim et al., 2011). Method of suppressing breast cancer cell by various HDAC inhibitors is represented in Figure 4.

Figure 4 Method of suppressing breast cancer cell by various HDAC inhibitors (see online version for colours)



6 Potential side effects of HDAC inhibitors

HDAC inhibitors are antineoplastic agents which are potentially used in cancer therapy. Although they are highly used as cancer therapeutics, they produce some side effects on continuation of the drugs. The side effects are eliminated with withdrawals of drugs. The common side effects are fatigue, nausea, dehydration, thrombocytopenia and neutropenia. Nausea, vomiting and anorexia are the most common higher grade side effects (Patnaik et al., 2002; Carducci et al., 2001; Camacho et al., 2007; Atmaca et al., 2007; Gimsing et al., 2008). Fatigue is a common side effect seen in case of HDAC I hibitors (Kummar et al., 2007; Olsen et al., 2007; Crump et al., 2008). Thrombocytopenia, neutropenia and anaemia have been observed in many cases. Thrombocytopenia is the most common hematologic effect especially in the case of Romidepsin and Vorinostat (Giles et al., 2006; Ellis et al., 2008; Kelly et al., 2005; Richardson et al., 2008). Febrile neutropenia is the result of Dacinostat inhibitors. LBH589Z is s novel HDAC inhibitor that inhibits proliferation and induces apoptosis. It induces nausea, vomiting, diarrhoea, hypokalemia, loss of appetite and thrombocytopenia. MGCD0103 is an isotype selective inhibitors of HDACs. This drug causes fatigue, nausea, vomiting and diarrhoea type symptoms (Siu, 2008).

Metabolic side effects have also been studied to HDAC inhibitors. Liver toxicities including elevation in liver transaminases and hyperbilirubinemia, hyperbilirubinemia were reported (Stadler et al., 2006; Piekarz et al., 2006). Renal dysfunction in the form of elevated creatinin levels infrequently with HDAC inhibitors (Blumenschein et al., 2008). Elevated Lactate dehydrogenase, hypertriglycerides and hyperglycemia were reported (Shah et al., 2006). Neurological events such as status epilepticus in association with uremia and parethesia resulted with belinostat (Ryan et al., 2005).

7 Development of resistance in cancer cell to HDAC inhibitors:

Acetylation and deacetylation of histone protein is associated with modulation of gene expression. Overexpression of HDACs has been reported in multiple forms of cancer. Despite the promising therapeutic value of HDAC inhibitors, drug resistance is a significant clinical issue (Lee et al., 2012; Robey et al., 2011). In the clinical studies the increased expression of multiple drug resistance genes MDR1, ABCB1 and its product p-glycoprotein were reported (Mickley et al., 1989). High levels of antiapoptotic proteins BCL-2, BCL-XL, MCL-1 have been reported. Understanding the mechanism of resistance development to HDAC inhibitors that are altered in drug resistant cells could help to develop strategy to overcome drug resistance.

8 Conclusions

Epigenetics plays an important role in regulation of gene expression. Histone deacetylases are enzymes known to induce changes in the structure of chromatin through which it prevents transcription factors to bind to the promoter region. When promoters are inaccessible to the transcription factors the gene remains suppressed. Breast cancer is one of the most common and dreadful forms of cancer all across the world women are

afflicted with. HDAC inhibitors could be crucial against breast cancer. HDAC inhibitors are under various phases of clinical trials showing ray of hope for the treatment of breast cancer. The success of HDAC inhibitors will motivate to design more specific and potent inhibitors to regulate breast cancer and diabetic associated disorders.

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Abbreviations

HDAC	histone deacetylse
PEPCK	phosphoenolpyruvate carboxykinase
HIF-1 alpha	hypoxia-inducible factor-1 alpha
VEGF	vascular endothelial growth factor
HER2	human endothelial receptor 2
CRTC2	CREB-regulated transcription co-activator2
G6Pase	glucose-6-phosphatase
GLUT4	glucose transporter4
MEF2	myogenic transcription factor 2
AMPK	AMP activated protein kinase
NuRD	nucleosome remodelling and deacetylating
BcoR	Bcl-6-interacting co-repressor.