Abstract: Breast oncogenesis is a multistage process that involves epigenetic and genetic changes. Epigenetics is outlined as reversible changes in gene expression, with no alteration in gene sequence. DNA methylation, histone modification, and nucleosome transformation are the foremost epigenetic changes that may get dysregulated in breast cancer. Epigenetic silencing of tumor suppressor genes (TSGs) is reversed by varied molecules as well as natural compounds like polyphenols which will act as a hypermethylation agent. Nowadays, much of the research is going in the direction of natural and dietary compounds and attempting to search out novel and extra effective medical aid for the breast cancer patients. In this literature, few vital natural chemical compounds effective against the breast oncogenesis with their mode of actions are discussed. Such chemicals act as an analytical and prognostic tool in breast cancer due to their role in epigenetic regulation.

Keywords: DNA methylation, Epigenetics, Gene expression, Oncogenesis, Tumor suppressor gene.

INTRODUCTION
Breast cancer (BC) is a community health crisis worldwide. BC remains the general melanoma in women globally and is the most important source of cancer-related mortality in females in developing and developed countries (Ferlay et al., 2008). In the UK, on a standard, 1 woman out of 9 develops this sickness in their lifecycle. There are numerous factors connected via the breast tumor growth, for example, gender, use of alcohol with high amount, diet (food), body movement, past of family history, lifestyle routine as well as endocrine aspects. In 2019, A Study evaluates 268,600 novel occurrences of invasive ductal carcinoma (IDC) that were diagnosed among women and roughly 2,670 cases were analyzed in...
men. In 2019, around 500 men and 40,000 women were died by breast cancer (American Cancer Society, 2019). Although breast cancer rates are higher among women in developed regions, but rates were increasing in almost each region worldwide. Over 3.8 million women with a history of breast cancer were still alive as on January 1, 2019 in US (Miller et al., 2019). Breast cancer characteristically has no symptoms when the tumor is little that is why screening is vital for primary detection. The foremost general physical sign is a painless lump. Occasionally, breast cancer spreads to underarm lymph nodes and causes a lump or swelling, yet before the novel breast tumor is large enough to be felt. Less common signs and symptoms like breast pain or heaviness; persistent alterations, like thickening swelling, or redness of the skin; and also, nipple size changes, like spontaneous discharge, scaliness, or retraction. Slight tenacious alteration within the breast must be accessed through a doctor. However, its sensitivity and specificity remains dissatisfactory (Radpour et al., 2011). In younger women, false-positive results are more common, who have previous breast biopsies, family history of BC and also who taking estrogen (Nelson et al., 2016 and Njor et al., 2011). Molecular biomarkers are novel approaches of indirectly & directly detect of human breast cancer (BC).

**EPIGENETICS AND BREAST CANCER**

Epigenetic silencing of (TSGs) tumor suppressor genes is emerging as a well-established oncogenic method with dynamic reprogramming. Epigenetic alterations of the genome include promoter methylation of DNA and chromatin remodeling that plays an important function in tumorigenesis. Current findings state epigenetic alterations as one of the key factors in breast cancer (Dworkin et al., 2009). These modifications are fairly interesting as targets for the therapeutics because of their potential for reversal. Proper medical care for breast cancer patients will likely to depend upon a better understanding of the role epigenetic alterations in carcinogenesis, merging with targeted treatments, to overcome resistance and recover sensitivity to treatment (Fig.1). Some of the epigenetic mechanisms that can contribute to breast cancer and tools that can be used to investigate these mechanisms and their response to drugs are being mentioned here (Fig. 2).

Fig.1: Application of epigenetic therapies in Breast Cancer.
METHODS TO IDENTIFY EPGENETIC ALTERATIONS

Gene specific epigenetic changes of breast carcinoma are probable to occur early in tumorigenesis and are possible to be used for early spotting and prevention (Balch et al., 2005). DNA methylation act as a biomarker for early detection of cancer. First, incidences of aberrant methylation of specific CpG islands are more than those of other alterations and methylation were often calculated through genome-wide screening. Secondly, aberrant methylation patterns were often detected even once they are entrenched in an intemperance quantity of usual DNA molecules. Third, methods for the recognition of methylation patterns are moderately simple (Wajed et al., 2001). As epigenetic modifications developed can be used as a biomarker for individualized carcinoma treatment and therapeutic intervention, it's important to know the various diverse methods obtainable for detecting the occurrence of methylation, histone modifications, and microRNAs (Balch et al., 2007). New promising high-throughput methylation detection methods are available which permit researchers and clinicians to spot an "epigenetic signature" specific to breast tumor. Diagnosis and categorization of carcinoma status involve biopsy to check the tumor size, histological grade, hormone receptor status, and HER2/Neu amplification. Hypermethylation of genes normally methylated in carcinoma in certain breast cancer patients has also been used to perceive early malignant transformations. Sera methylation are frequently detected using methylation-specific polymerase chain reaction.

Although, epigenetic alterations involve chromatin but they aren't yet used clinically for carcinoma detection, future panels of epigenetic chromatin modifications could also be incorporated into standard tests. One technique used to detect is chromatin remodeling that could be a combination of chromatin immunoprecipitation (ChIP) and PCR, which permits for quantification of the protein binding to a particular region of DNA (Dworkin et al., 2009). ChIP-chip associations, chromatin immunoprecipitation with array technology allows interrogation of thousands of promoter elements. In the newest technology ChIP-seq, ChIP was associated with novel generation sequencing, is highly quantitative and not biased by which features that were in an array. Results from ChIP-seq-based studies are already leading to the identification of new genomic elements, showing epigenetic regulation in cancer (Feng et al., 2008).
HYPERMETHYLATION STATUS IN TSGs

APC

Adenomatous polyposis coli (APC) is a protein that in humans is encoded by the APC gene. APC is located at chromosome 5q21-22 and holds 15 exons. Its tumor-suppressing action is considered to be based on regulation of the intracellular effect of beta-catenin inside the Wingless/Wnt signal transduction mechanism (Fodde et al., 2001). Somatic APC alterations were investigated in only some of breast cancers (Furuuchi et al., 2005), despite high rates of allelic loss at chromosome locus 5q21 (Thompson et al., 1993 and Medeiros et al., 1994). However, epigenetic inactivation of APC due to DNA methylation is frequently present in both breast cancer cell lines as well as breast cancer tissue. In most cultured breast carcinoma cells, there is an absolute concordance between APC promoter methylation and silencing of its transcript (Virmani et al., 2004). Cellular APC expression can be restored after demethylation with 5-aza-2'-deoxycytidine treatment. The occurrence of APC methylation in primary breast tumors increases with size and tumor phase (Virmani et al., 2004; Roa et al., 2004; Chen et al., 2007; Liu et al., 2007). Furthermore, hypermethylation of APC was found in breast aspirate fluid DNA [20] and serum DNA from patients with pre-invasive and primary stage of breast cancer (Dulaimi et al., 2004).

Epigenetic inactivation due to hypermethylation was well established for APC in breast carcinoma, but as yet, few studies have addressed whether epigenetic alterations of the APC gene might characterize specific breast cancer phenotypes. Inflammatory breast cancer (IBC) has been infrequently studied that make distinct it from other forms of locally advanced breast cancer in the past, despite variances in age-specific incidence rates, clinical demonstration, histology, hormone receptor status and, to end with prognosis (Lerebours et al., 2005).

BRCA1

Breast cancer type 1 susceptibility protein is a protein in humans that is encoded by the BRCA1 gene (similarly called as a caretaker gene). The BRCA1 gene was cloned in 1994, as well as identified by “Y. Miki” on chromosome 17q12-21 after an intensive global effort (Miki et al., 1994). BRCA1 deficiency caused either by germ-line mutations or by down-regulation of gene expression, leads to tumor formation. Decreased expression of the BRCA1 gene has been contributed in both inherited and sporadic breast cancer, and the magnitude of the decreased correlates with tumor progression (Wirisma et al., 2018). It was informed that DNA methylation was the major cause of transcriptional silence of BRCA1, ranging from 13–40% in sporadic breast cancer (Butcher et al., 2007). Breast cancer, which has hypermethylation on BRCA1 promoter region are more likely to be of high grade or estrogen-receptor negative, and p53 positive (Johannson et al., 1997). It has been hypothesized that breast cancer, which has hypermethylation on the BRCA1 promoter region is more aggressive. Hypermethylation of the BRCA1 factor promoter is present in 56 % (78 of 139) of Taiwanese ladies with early-stage sporadic breast carcinomas, that is considerably above antecedently rumored frequencies for this alteration in present sporadic breast tumors (Hsu et al., 2013).

CDH1

The CDH1 (E Cadherin) gene is instructed in the transmembrane glycoprotein or integral membrane protein. In epithelial tissues, E-cadherin is significant in maintaining homophilic cell-cell adhesion. CDH1, a Ca++ dependent transmembrane glycoprotein functions in cell-cell adhesion placed in 16q22.1, is one of the cardinal regulators of morphogenesis (Overduin et al., 1995). CDH1 is involved in upholding cell-to-cell adhesion and also is observed as a suppressor of cellular invasion (Hazar et al., 2004). CDH1 methylation and loss of E-cadherin mRNA expression predominates in primary tumors with a more aggressive phenotype (high tumor stage and high histologic grade). It was also shown that promoter methylation of CDH1 is considerably associated with the CDH1 expression level, which was previously suggested by a limited number of studies (Graf et al., 2000).

The hypermethylation ofCDH1 promoter was shown to be an alternative mechanism of gene silencing in together primary breast carcinomas and breast cancer cell lines (Katarina et al., 2012). The methylation profile of CDH1 promoter was investigated in detail by Graf and its colleagues.
(Graff et al., 1997). They were the first to show the importance of CpG island 3, the region surrounding the CDH1 transcription start site, for CDH1 silencing (Shinozaki et al., 2005 and Caldeira et al., 2006). Subsequently, this part of promoter was used for evaluation of CDH1 methylation in many laboratories. The hypermethylation of this region was frequently observed in invasive breast carcinomas and it was significantly associated with the reduction of mRNA and protein expression (Celebiler et al., 2010).

RAR-β2

Loss of the appearance of nuclear retinoid receptors since the 1990s, including RAR-β2, in a variety of cancer cell lines has been detected by northern blotting or reverse transcriptase polymerase chain reaction (RT-PCR) technique (Hu et al., 1991). The human retinoic acid receptor beta2 (RARβ2) is a member of the nuclear receptor super-family and plays a key function in modulating the property of retinoic acid (RA) on cell development and variation (Hayashi et al., 2003). RARβ2 is an isoform of the RARβ gene transcribed by the P2 promoter located at 3p24. Methylation of the RAR-β2 gene promoter, along with methylation of other gene promoters, has been evaluated as a biomarker of breast cancer risks (Lewis et al., 2005).

The RAR-β2 promoter hypermethylation had a significant association with the susceptibility of breast cancer, in which the breast cancer group had a higher frequency of RAR-β2 promoter hypermethylation than normal tissue. Significant associations of RAR-β2 promoter hypermethylation with lymph node metastasis and (Tumor, Node, Metastasis) TNM-stage of breast cancer were found (Ming et al., 2018).

WT1

WT1 (Wilms' tumor suppressor) was first identified in 1990, as a tumor suppressor gene by positional cloning on chromosome 11p 13 in association with Wilms' tumor, a nephroblastoma common to children (Call et al., 1990). The WT1 gene is known to express four splice variants, each approximately 3 kb in length (Gessler et al., 1990). As nuclear transcription factors, the WT1 proteins modulate expression of a variety of growth factors and their receptors (Rauscher, 1993). Recently, WT1 protein was found to be present in normal breast tissues, but was absent or greatly reduced in a subset of primary breast tumor (Silberstein et al., 1997). It has been reported that hypermethylation of the WT1 CpG island was associated with silencing of full length (or normal) WT1 mRNA expression in MCF-7 and MDA-MB-231 breast cancer cells (Douglas et al., 1999).

EPIGENETIC REVERSAL IN BREAST CANCER DUE TO NATURAL COMPOUNDS

Natural compounds or phytochemicals present positive health compensation by acting overtly on specific molecular targets like genes, or by indirectly stabilizing conjugates that have an effect on metabolic pathways.

In carcinoma, abnormal histone modifications like acetylation and methylation of histone together with DNA hypermethylation were related to epigenetic silencing of tumor suppressor genes (TSGs) & genomic instability (Miki et al., 1994 and Neuhausen et al., 1994). During this context, the readers are recommended to seek advice from some recent reviews describing the useful roles of epigenetics and also the attainable epigenetic targets that altered expressions and are usually related to the carcinoma development and progressions (Eisinger et al., 1996 and Lane et al., 1995). Accumulating confirmation showed that natural phytochemicals together with the secondary metabolites originate within the dietary foods has the potential to remodel the epigenetic events and reverse the epigenetic changes before inflicting cancer progression (Wooster et al., 1994). Variety of phytochemicals like ginsin, curcumin, apigenin and also lycopene was reported to inhibit synthesis of metabolic product like prostaglandins and leukotrienes and, consequently, are thought to be effective therapeutic agents against cancer.

Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)1,6-hepta-diene-3,5-dione], the active ingredient of turmeric (Curcuma Longa Linn), is identified as a polyphenolic compound and has a very widespread medicinal activity as well as anti-breast-cancer activity. Curcumin significantly suppressed tumor growth and is also thought to be one of the chemo preventive agents (Gong et al., 2006).
Curcumin may perform as a DNA methylation inhibitor in breast cancer cells (Jiang et al., 2015; Zheng et al., 2014; Link et al., 2013). However, curcumin’s probable as a polymer methylation inducer remains to be totally explored. Another study, Al-Yousef and groups incontestable that curcumin exhibits contradictory purposes with reference to polymer demethylation, methylation & re-expression of the tumor-suppressor factor BRCA1 polymer repair associated (BRCA1). In addition, because the methylation and suppression of the expression of oncogene cistron synuclein (SNCG) in carcinoma cells (AL-Yousef et al., 2020). In this study, incontestable that the foremost tested curcumin concentrations (10 and 20 µM) will enhance the protein and mRNA levels of 1 present hypermethylation suppressed TSG RASSF1A in each MDA-MB-231 and MCF-7 cells. In MCF-7 cells, RASSF1A reactivation is a minimum of part related to its promoter hypomethylation (25% decreases). The hypomethylation activity of curcumin is probably from twin functions of curcumin on DNMT1: the chemical inhibition of DNMT1 and also the biological downregulation of DNMT1 (Du et al., 2012). This finding that curcumin inhibited DNMT1, thereby reactivating RASSF1A through its promoter hypomethylation, represents a unique molecular machinery of its antitumor chemopreventive activity for carcinoma.

Recently, Manson et al. accordingly extended the treatment with curcumin (<3 µM) leads to altered gene expression; as an example, E-cadherin-11 and reduced growth of cancer cells in MDA-MB-231 cells, just like that evoked by nucleoside DNA methylation inhibitors (Moiseeva et al., 2007). Additionally, many hypermethylation silenced TSGs, as an example, GSTP1 (Ramachandran et al., 2005) and MGMT (Niture et al., 2007), are reportable to be reactivated in carcinoma or different cancer cell lines. Consequently, collective information recommends that curcumin will induce polymer hypomethylation and activate hypermethylation silenced genes. In addition, another study concluded that treatment of carcinoma MCF-7 cells with curcumin for complete at complete causes complete reversal of GSTP1 promoter hypermethylation and results in the re-expression of GSTP1 protein (macromolecule) suggesting curcumin to be a wonderful nontoxic hypomethylating agent. Curcumin at lower concentration causes reversal of hypermethylation of GSTP1, and at higher concentration (20 and 30 µM) re-expression of GSTP1 decreases due to hormesis (Kumar et al., 2017).

**Epigallocatechin-3-gallate**

Epigallocatechin-3-gallate (EGCG), also acknowledged as epigallocatechin gallate, one of the phenolic catechins present in green tea and is widely known for its health-related benefits. It was originated that EGCG has epigenetic effects in carcinoma cell line either by demethylation or suppressed methylation of the promoters of tumor suppressor genes (TSGs).

Although hypermethylation of gene promoters related to gene silencing, there are exceptions to the current rule like the hTERT (human enzyme reverse transcriptase), a promoter that, paradoxically, is extremely methylated in most neoplasm cell varieties, rendering hTERT active. Treatment with EGCG can also inhibit factor expression through influencing the DNA methylation status of those genes. Meeran et al., (2007) have shown that treatment with EGCG inhibited the transcription of the tumor-promoting factor hTERT, the catalytic subunit of the enzyme, through epigenetic mechanisms in ER+ MCF-7 and ER-MDA-MB-231 cells. Berletch et al., (2008) reported that treatment of MCF-7 cells with EGCG resulted in reduced hTERT messenger RNA expression. Moreover, downregulation of hTERT gene expression in MCF-7 cells perceived to be mostly due to epigenetic alterations, as proved by the time-dependent decrease in hTERT promoter methylation (Berletch et al., 2008).

Recent researches recommend that EGCG could prevent carcinogenesis by multiple epigenetic processes, together with DNA methylation and histone acetylation (Gianfredi et al., 2017 and Li et al., 2017). Another study investigated the phenotypic impact of tea catechins on human carcinoma cells and processed the epigenetic mechanism of however EGCG regulated the DNA methylation of the SCUBE2 gene. EGCG will reverse the DNA methylation standing and
activate the expression of the SCUBE2 factor by reducing DNMT expression and activity in human breast cancer cells, MCF-7 and MDA-MB-231 (Sheng et al., 2019).

Another study, provided proof that, EGCG will induce re-expression of endogenous estrogen receptor α (ERα) in ERα-negative MDA-MB-231 breast cancer cells. For the primary time, our results clearly show that this purposeful, useful reactivation by EGCG treatment is a minimum of partially regulated via epigenetic mechanisms, particularly through chromatin remodeling and additionally found that this result was synergistically increased once EGCG was combined with the deacetylation substance, TSA, indicating simple protein modification plays a crucial role in EGCG-induced useful reactivation (Li et al., 2010). EGCG will restore useful expression by regulatory epigenetic mechanisms, and this result is increased once combined with an HDAC substance and additionally effective uses of combination approaches in carcinoma medical aid and can facilitate to explore simpler chemotherapeutic ways toward hormone-resistant carcinoma. Epigenetic mechanism of the EGCG molecule provides a scientific basis for the additional application of EGCG within the treatment of human breast cancer.

**Genistein**

Genistein is an isoflavone that is represented as an angiogenesis inhibitor and a phytoestrogen, found to suppress the uncontrolled cell growth of cancer. It had been 1st separated in 1899 from the dyer’s broom. Isoflavones like genistein is initiated during a variety of plants as well as ligneous plant, soybeans, fava beans, and being the first food supply.

The study demonstrated that continual dosing with 3.125 μM genistein part demethylates the promoter of the GSTP1 gene and will increase its expression in MDA-MB-468 carcinoma cells. Additionally, studied whether or not genistein could demethylate any hypermethylated genes in MCF10A breast cells, MCF-7 and MDA-MB-468 breast cancer cells and also determined that one’s treatment with genistein demethylates the RARβ2 cistron in MCF10A cells, however very little result was known about the GSTP1 gene in MCF-7 or MDA-MB-468 breast cancer cells (King-Batoon et al., 2008).

**Lycopene**

Lycopene is the major carotenoid belonging to tetra terpenoids and a phytochemical, in some fruit and vegetable like red carrots, watermelons, tomatoes etc. Lycopene is non-poisonous and normally found in the diet. The anticancer activities of lycopene progress through regulation of growth factor signaling, apoptosis induction breast cancer cells and changes in phase II detoxifying/antioxidant enzyme (T. R. Holzer et al., 2006; N. Chalabi et al., 2006; Lian F. et al., 2008). In addition, lycopene inhibits tumor cell invasion, metastasis, and angiogenesis, thereby suppressing the improvement and enlargement of cancers. King-Batoon et al. established the action of lycopene in breast cancer cell lines on GSTP1 gene (King-Batoon et al., 2008). It was experimented that lycopene (2µM for single week) upregulates the appearance of GSTP1 and has the capability to demethylate GSTP1 promoter in MDA-MB-468 cell line. The expressions of additional genes such as HIN1 & RARβ2 persisted unchanged by lycopene therapy in MDA-MB-468 and MCF-7 breast cancer cell lines (King-Batoon et al., 2008 and Bishop et al., 2015).

**Resveratrol**

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a sort of natural phenol produced by numerous plants. Resource of resveratrol in diet food includes raspberries, blueberries, peanuts and mulberries. Resveratrol has been recognized as potent anti-inflammatory, anti-aging, and chemo preventive agent. Bhat et al. showed that (Bhat et al., 2001), within the presence of E2, resveratrol acts as associated antiestrogen and an antagonist within the non-appearance of E2 in several carcinoma cell lines. Qin et al. reportable that resveratrol acts as DNMT 3b substance and reduces and reduces methylation with increasing current resveratrol and it conjointly suppresses expression of the androgen receptor (Qin et al., 2014). By considering cellular targets associated with epigenetic pathways, SIRT1 and acetyl radical enzyme p300 were reportable to be activated by resveratrol (Bishayee, 2009 and Wang et al., 2008).

A study was performed on a genome-wide DNA methylation analysis supported promoter DNA microarrays in MDA-MB-231 cells treated with
dietary resveratrol. As an example, resveratrol prohibits the expression and activity of DNA methyltransferase 1 (DNMT1) in carcinoma cells, that impairs the epigenetic silencing of the BRCA1 neoplasm suppressor by modulating acetylation of H3K9, and H4, association of mono-methylated-H3K9, DNMT1& methyl binding domain protein-2 with the promoter of BRCA-1 factor (Li et al., 2014). On the opposite hand, resveratrol conjointly exhibits epigenetic actions by targeting the chromatin modifier MTA1, histone deacetylases (HDACs) and specific microRNAs (Dhar et al., 2014). Alternative investigate recommends that the histone H2B ubiquitin ligase RNF20, a chromatin modifying catalyst and supposed neoplasm suppressor, is an epigenetic target of resveratrol in carcinoma cells (Gao et al., 2011). However, the advances within the data of epigenetic modulation by resveratrol in cancer area unit still scarce. The transcriptome of MDA-MB-231 cells exploitation was analyzed conjointly of 100μM resveratrol at 24 and 48 hours (Medina et al., 2016), that leads USA to correlate the epigenetic changes with gene expression variations at messenger RNA level and to outline however these restrictive mechanisms impacts on expression of specific oncogenes and neoplasm suppressor genes over time course.

**Sulforaphane**

Sulforaphane (SUL), a plant chemical and is also one in all nature's marvelous compounds. It's found in cruciferous (dilleniid dicot family) vegetables like Brussels sprouts, broccoli and cabbages.

Emerging proof suggests that SFN could alter further epigenetic processes within the breast and prostate together with DNA and histone methylation in addition as ncRNAs. DNA methyl transferases (DNMT) add methyl groups (—CH3) to cytosine bases in DNA. High levels of DNA methylation were typically related to gene silencing. DNMT1, usually remarked because the “maintenance” DNMT, maintains methylation patterns through cellular division. In distinction, DNMT3a and DNMT3b area unit accountable for de novo methylation and methylate DNA throughout development and per environmental signals (Perry et al., 2017). As a consequence, attenuated international and site-specific DNA methylation was connected to transformed gene expression (Meeran et al., 2012; Pledgie-Tracy et al., 2007; Meeran et al., 2010). SFN could be a promising dietary chemopreventive agent because of its ability to focus on multiple pathways concerned in carcinogenesis.

**CONCLUSION**

Breast cancer is a general category of malignancy with a substantial morbidity rate as well as rate of mortality among women. Cancer patients usually experience unusual kinds of treatment approaches. On the other hand, herbal treatments because of their lower side effects have attracted a huge deal of attention. Natural compounds, a plant extract with herbal origins are the most commonly used compounds for the therapy of a wide range of breast cancers. Examination of histologically standard tumor restrictions for epigenetic modification and field cancerization will enhance the capability to eliminate all “pre-cancerous” tissues and reduce local recurrences. As we recognize specific epigenetic modifications contributing to breast oncogenesis and diagnosis, these findings will lead to significant advances for breast cancer (BC) treatment options. These natural compounds are a significant factor of our diet and therefore do not have any cytotoxic special effects on common cells unlike the demethylating chemicals. The reversal of these epigenetic transforms by natural compounds could establish to be significant in the direction of therapy of cancer. Newer description of those medications is probably going to play an essential aspect in upcoming clinical therapy. Subsequently, epigenetic modifications also can be used as biomarkers; targeted treatments could sometimes be used as preventive measures.

**CONFLICT OF INTEREST STATEMENT**

The authors declare that there is no conflict of interest.

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