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Role of *Coccinia indica* in the prevention and management of breast cancer: A review

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ABSTRACT

Cucurbitacin B is isolated from the fruit of *Coccinia indica*, have reported for treatment of several types of cancer due to its anticancer and antioxidant effect. Cucurbitacin B, inducing cell cycle arrest at G2/M as well as apoptosis. It can act as anti-proliferative agent for breast cancer cells *in vitro* and *in vivo* and reduces the ferrocynaide to ferrous. Cucurbitacin B inhibits telomerase activity in several breast cancer cell lines through down regulation of both the hTERT and c-Myc expression. The expression of the hTERT gene directly depends on the telomerase activity as the hTERT protein, is the catalytic rate-limiting determinant subunit of telomerase. Estrogen receptor activates a number of cellular signal transduction and also ERK/MAPK pathway. It leads to the translocation of activated MAP kinase to the nucleus where it regulates the expression of a number of transcription factors. Including pertinently, c-Myc but when cell lines treated with cucurbitacin B, directly modulates either the estrogen receptor or subsequent signalling pathway and the down regulate JAK/STAT pathway. Whereas some different biological pathway exist in estrogen negative cells, where c-Myc is primarily controlled at the level of RNA stability. However, cucurbitacin B exerts anticancer activity and inhibit the telomerase and induced apoptosis.

Keywords: Breast cancer, telomerase, hTERT, c-Myc, estrogen positive, estrogen negative, cell line, cucurbitacin, (-)- epigallocatechin-3- gallate, breakage–fusion–bridges, ataxia-telangiectasia.

Highlights

- Cucurbitacin B is isolated from fruit of *Coccinia indica* able to the down regulated the expression of telomerase and leading to suppressed viability of the breast cancer cell line (MCF-7) and induce apoptosis.
- The activation of the non-homologous end joining (NHEJ) pathway leads to end-to-end fusions that initiate cycles of breakage–fusion–bridges.
- Mutation also transpire in some other gene like ATM and p53 promotes to ataxia-telangiectasia and cause Li-Fraumeni hereditary syndromes, respectively.

INTRODUCTION

Globally, the rising incidence of breast cancer makes the most common lethal malignancy among females. Approximately one out of ten women and its rising incidence makes a major public health problem [1,2]. It is more common in the Western countries than in Africa, South America or Asia. It is also higher in developing country as compared to developing ones [3]. BC develops from breast tissue and associated with some symptom & signs like a lump in the breast, a change in breast shape. Including dimpling of the skin, secretion of fluid from the nipple, or a red scaly patch of skin, bone pain, swollen lymph nodes and shortness of breath, or yellow skin (Fig-1) [4]. Indeed, the risk of developing breast cancer after 65 years of age is 5.8 times higher than before 65, and 150-fold higher than before 30 years of age. As well as other risk factor such as female sex, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not

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at all and family history. However, excessive exposure to estrogens and deficiency of genomic integrity causes BC. Mostly, BC develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk [4].

Molecular Mechanism of Breast Cancer

Like other cancers, breast cancer is also occurring because of interaction between an environment and genetic factor. Approximately, 15% of BC cases are thought to be hereditary, meaning that they result directly from genetic mutation and innate from a parent. It also arises from germ-line mutations in high-penetrance of BC with associated gene mutation including BRCA1 and BRCA2. Recently, BRCAs are associated with lethal risk of the disease and in the 70 years age of the female. A recent report has suggested that 65% of BC arises due to BRCA1 and only 45% BRCA2 mutation [5-6]. However, BC represents a conventional hereditary disease and follow the Mendelian mode of transmission [7]. Although, mutation also transpires in some other gene like ATM (ataxia telangiectasia mutated-normally helps repair damaged DNA) and p53 (stop the growth of abnormal cells), promotes to ataxia-telangiectasia and cause Li-Fraumeni hereditary syndromes, respectively. It may also be causing genetic defects in the breast cancer cell. These genes are increased incidence of breast neoplasia in their heterozygous carriers. These genes are causes rare gene mutations and often do not increase the risk of breast cancer as much as the BRCA genes [8]. Normally, the healthy cells will always be committed to apoptosis (cell suicide) when they are no longer needed whereas in cancer condition, the cells are confined from cell suicide or apoptosis by more than a few protein clusters and mutated pathways. Usually, these two most central signalling pathways - PI3K/AKT and RAS/MEK/ERK (fig-2) are involved in the maintenance of cell cycle and in normal condition, the PTEN protein "Turns off" the PI3K/AKT pathway when the cell is ready for cell suicide. Although when both signalling pathways are mutated along with gene defect, which turns them permanently "On", rendering the cell incapable of committing suicide when it is no longer needed and arise cancerous condition. In case of BC, the gene for the PTEN protein is mutated and do not "Turns off" the PI3K/AKT and RAS/MEK/ERK pathway; therefore, the cancer cell does not undergo for apoptosis process [9].

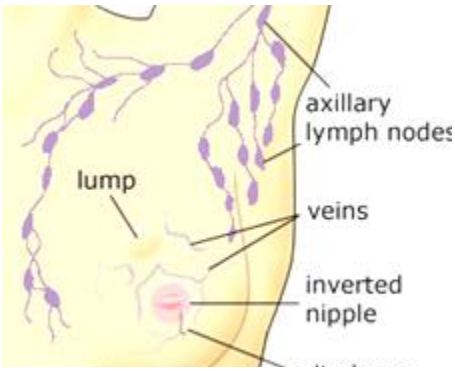

Figure 1: Showing the breast cancer symptoms and signs. (Source http://www.geronguide.com/gallery/index.php/Breast-Cancer/breast-cancer-symptoms-signs)

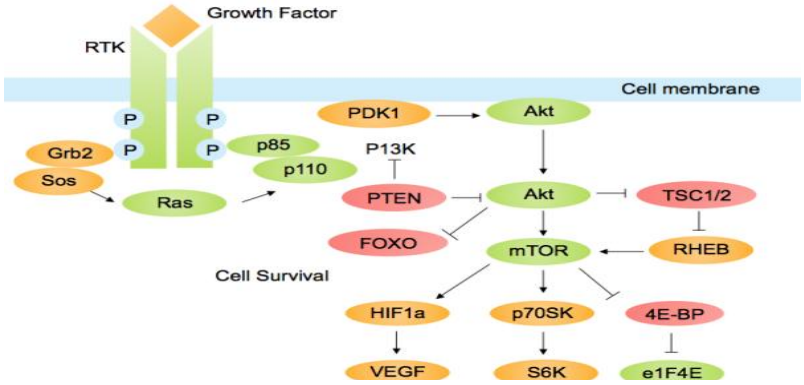

Figure 2: "Turn on" signalling pathway, proteins involved in breast cancer cells. Oncogenes (activation increases in cancer) are green and tumour suppressors (inactivated or lost in cancer) are red (Source: http://www2.hawaii.edu/~joeramos/research.html).

Several other studies have also reported the interaction between various promoting risk factors with genetic material leads to accumulation of somatic cell mutations in breast epithelial cells. Gross chromosomal abnormalities cause chromosomal instability, appears in breast cancer genome [10]. Numerous studies have reported that telomerase is the enzyme, responsible for maintaining telomeres at the end of a chromosome. Telomeres is heterochromatic structures, contain a double-stranded DNA region with TTAGGG tandem repeat sequence at the ends of chromosomes that protect the chromosomes from end-to-end fusion, rearrangement and translocation and a 150–200 nucleotide-long G-rich single strand [11]. However, it plays a protective role in cell proliferation, against end-replication problems by adding TTAGGG repeats to the telomeres and associates with telomere binding proteins form the sheltering complex (Figure 3). This structure protects linear chromosome ends from recognition as DNA double-strand breaks (DSBs), consequently contributing to genomic stability and highly active only in germ cells and in tissue stem cells [12]. The G-rich strand extension raids the doubled-stranded DNA region of the telomere to form a protective telomere T-loop. This is bound by the shelterin complex, comprising the telomeric repeat binding factor 1 (TRF1), TRF2, repressor-activator protein 1 (RAP1), protection of telomeres protein 1 (POT1), TIN2 organizing protein (TPP1), and TIN2[13-14].

POT1 binds to the 30 singled-stranded overhang of the DNA repeats, and TRF1 and TRF2 bind to telomeric double-stranded DNA. TIN2 then binds TRF1 and TRF2 and recruits the TPP1–POT1 complex and form DNA capping structure [11,13-14]. In normal somatic cell DNA polymerase cannot completely replicate the 5'end of the lagging strand, leading to telomere shortening with each cell division due to the low level of telomerase and this telomere shortening triggers the cell to undergo replicative senescence, cell cycle arrest and DNA damage signalling [14]. Studies have reported that telomerase consists of two core subunits, essential for its activity- one is the human telomerase RNA template (hTERC) and another one is the catalytic subunit of human telomerase reverse transcriptase (hTERT). It recognizes the 30 hydroxyl groups at the end of the G-rich overhang and elongates the telomere [15-16]. Strongly, telomerase expression associated with neoplastic growth and cancerous cells that may be a necessary step for tumor or cancer progression. Various studies have reported, telomerase is highly expressed up to 95% in BC, but the expression is down in normal breast tissue [17-20]. In BC, telomeric DNA is uncapping and the loss of normal telomere structure due to either the loss of telomeric (TTAGGG) repeat sequences or alteration in telomere proteins. Oncogene-induced replicative stress may include the intrinsic telomere shortening. This is associated with cell replication and dysfunctional telomeres reduce number of alterations such and a DNA damage response (DDR) through the activation of upstream kinases, including DNA-dependent protein kinase (DNA-PK), the ataxia telangiectasia mutated (ATM) and ataxia telangiectasia related (ATR) kinases. In addition, the DDR can have two contradictory effects depending on the status of checkpoints usually mediated by tumor suppressor genes like p53 and p21. During tumorogenesis, p53 activation induces cell cycle arrest, apoptosis, or senescence, negatively affecting the stem cell functionality and causing tissue degeneration. In p53-deficient cells, the damage proceeds unrestricted along with the activation of the ATM and ATR kinase pathways. It leads to mitotic wedge; cells can then bypass mitosis and re-enter the S-phase of the cell cycle and becoming polyploidy (PP). PP contain multiple centrosomes, it may be lead to genomic instability, will give rise to the random distribution of chromosomes. PP are also

creating aneuploid daughter cells during mitosis. Reported have shown the activation of the non-homologous end joining (NHEJ) pathway leads to end-to-end fusions that initiate the cycles of breakage–fusion–bridges. Upon telomere healing, either by telomerase reactivation or by homologous recombination-based mechanisms, indefinite cell cycling is allowed, and stable malignant clones can be generated [11-16,21]. Therefore, an increase in telomerase activity is often straight correlated with the uncontrolled growth of cells, which is a known hallmark of breast cancer. Hence, need for development of such a agent, having activity against telomerase that may be a useful approach to cure BC through the inhibition of cancer cell proliferation and develop novel breast cancer therapies [22].

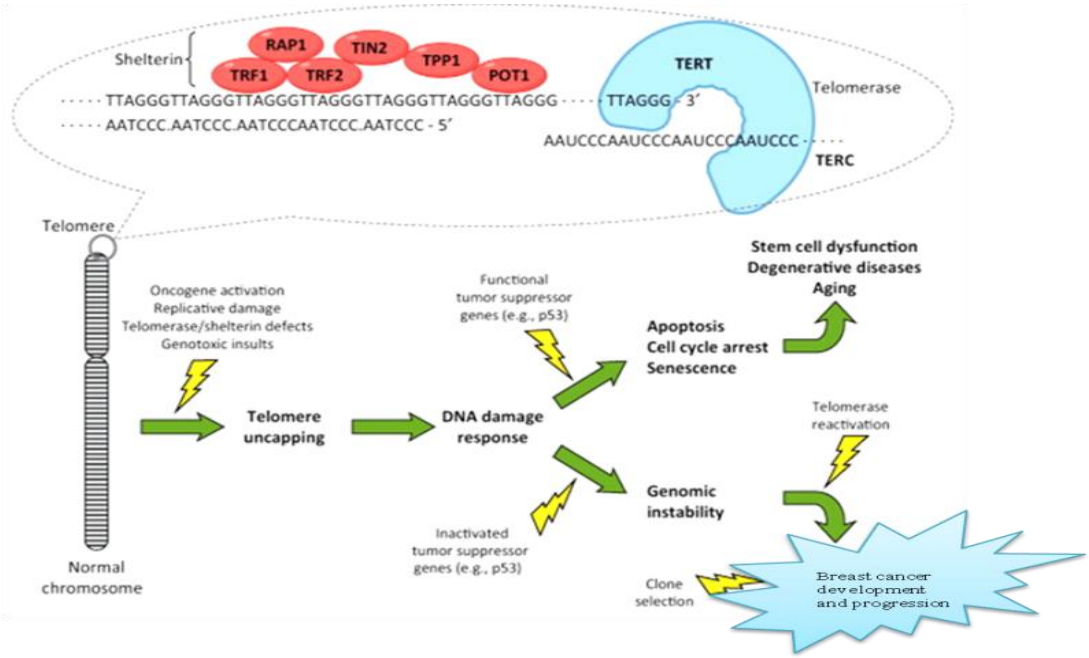

Figure 3: Telomeres telomerase, and their relationship to breast cancer development and progression [15].

Anticancer and Antiproliferative Effects of Cucurbitacin B

In traditional medicinal system, herbal extracts have been used against several cancer types such as breast, lung, colon, pancreatic and ovarian cancer due to its anticancer, antioxidant and antiproliferative effect over the cancerous cells and inducing cell cycle arrest at G2/M as well as apoptosis in the cancerous cells. A large number of conventional chemotherapeutic drugs are available with high toxic effect and often result in drug resistance after a certain period. For this reason, need to develop the some other alternative drug, based on the natural source [15,21-22]. Several studies have shown Costunolide a natural sesquiterpene compound and first time isolated from the bark of Magnolia sieboldiiin in 2005 by Choi and colleagues. They have observed, Costunolide can reduce the activity of telomerase and able to inhibited the growth of a human breast cancer cell line [23]. Similarly some other natural bioactive molecules- curcumin, found in the rhizomes of *Curcuma longa* L., can also inhibit activity of telomerase by down-regulating hTERT expression in MCF-7 breast cancer cells [24]. Recently, some other bio active molecules have discovered from plants,(-)-epigallocatechin-3-gallate (EGCG) is a constituent of green tea able to the down regulated the expression of telomerase and leading to the suppressed viability of the breast cancer cell line (MCF-7) and induce apoptosis [25]. Similarly, other bioactive molecule from herbal extract such as cucurbitans is highly oxygenated, tetracyclic triterpenes containing the cucurbitane nucleus skeleton. These are predominantly found in plants of the family cucurbitaceae similar to Brassicaceae, Scrophulariaceae, Begoniaceae, Elaeocarpaceae, Datiscaceae, Desfontainiaceae, Polemoniaceae, Primulaceae, Rubiaceae, Sterculiaceae, Rosaceae, Thymelaeaceae and in some mushrooms. *Coccinia indica* (*C. indica*) (fig-4), members of which have long been used in oriental medicines [26-27].

C. indica is also known as -little gourd or Rantondli in Marathi, Bimba in Sanskrit and Kanduri ki bel in Hindi. It is indigenous to Bengal and other parts of India. It grows abundantly all over India, tropical Africa, Australia, and Fiji and throughout the oriental countries. The plant has also been used extensively in Ayurveda and Unani practice in the Indian subcontinent [28]. In India use of the different parts to cure specific ailments has been in vogue since ancient times. The indigenous system of medicine, namely, Ayurveda, Siddha, and Unani has been in existence for several centuries [28]. Therefore, it has been used in traditional medicine for centuries [29-30]. Phytochemical studies conducted on plants of this family have led to the isolation of numerous bioactive compounds such as alkaloids, glycoside and saponin, bamyrine, lupeol, cucubbitacin, cephalandrol, cephalandrine and flavonoids, taraxerone, taraxerol, B-carotene, lycopene, cryptoxanthin [31-32]. Cucurbitacins have a broad range of biological effects, including anti-inflammatory, hepatoprotective and anticancer activities [33]. The studies suggest it have different variances and arbitrarily divided into twelve types, the cucurbitacin A to T [33,26]. These different forms of cucurbitacin have been studied in vitro and in vivo for their anticancer effects [33]. The type of cucurbitacin compound like cucurbitacin E, involved in the treatment pancreatic and prostate cancer by its anti proliferation nature. It can inhibit the viability of pancreatic (PANC-1) and prostate cancer cells and induce apoptosis via suppression of STAT3 phosphorylation and up-regulation of p53 [33-34]. Cucurbitacin E, also causes disruption of the cytoskeleton structure of actin and vimentin [35-37]. Like cucurbitacin E, cucurbitacin I inhibit nasopharyngeal carcinoma cell (NPC) proliferation and invasion. It can also inhibit NPC tumor formation in nude mice and can also inhibit STAT3 phosphorylation [33,38]. Several studies have shown that in several breast cancer cell lines, such as T47D, SKBR-3, and MCF-7, cucurbitacin B and E glucoside combination as well as each of them can induce cell cycle arrest in the G2/M phase by reducing the amount of p34CDC2/cyclin B1 complex [37]. During treatment, these bio active molecules caused morphological changes in the breast cancer cell through the impairment of actin filament organization and can induce apoptosis in Bcap37 breast cancer cells [33-41]. Most abundant forms of Cucurbitacin, Cucurbitacin B, (fig-5) (isolated from the fruit of *C. indica*), have the potential to be used as a favourable phytochemical for breast cancer management and treatment [21]. Cucurbitacin B continues to be structural improvement in the future chemotherapeutic approach [42]. It has been shown to have

antioxidant, anticancer [21] and anti-inflammatory activities [43]. It can act as anti-proliferative agent of breast cancer cells *in vitro* and *in vivo* [21] including analgesic, antipyretic activity [43-45] and hypoglycaemic activity [46]. Another studies have observed cucurbitacin B and dihydrocucurbitacin B, both can inhibit the growth of breast cancer cell liness and reduces the ferrocynaide to ferrous [47-48].

Figure 4: *Coccinia indica*

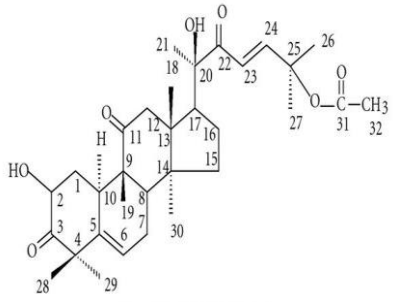

Figure 5: Chemical structure of Cucurbitacin B

Some studies have reported, cucurbitacin B inhibits growth of breast cancer cell by apoptosis pathway and also inhibit telomerase activity in several breast cancer cell lines through down regulation or inhibit both the hTERT and c-Myc expression in breast cancer cells. It has inhibitory effect on the estrogen receptor (ER)-negative breast cancer cells SKBR-3 [49]. The expression of the hTERT gene is directly depend on the telomerase activity as the hTERT protein is the catalytic rate-limiting determinant subunit of telomerase [50]. During process of transcription in the breast cancer cells, c-Myc factor binds to E-box (CACGTG) and promotes expression of the hTERT gene and upregulates telomerase by enhancing hTERT expression whereas cucurbitacin B might exert anticancer and anti-proliferative effects over the all breast cancer cell line via reduced the telomerase activity [51]. Some other finding related to estrogen positive and estrogen negative breast cancer cell line cucurbitacin B can suppress the viability of cancer cells via different biological pathways. Cucurbitacin B can also down regulate the expression of hTERT and c-Myc in the estrogen positive cell lines like T47D and MCF-7 [49]. In these cell line, presence estrogen receptor activates a number of cellular signal transduction and also ERK/MAPK pathway. It leads to the translocation of activated MAP kinase to the nucleus where it regulates the expression of a number of transcription factors. Including pertinently, c-Myc [50] but when cell lines treated with cucurbitacin B, directly modulates either the estrogen receptor or subsequent signalling pathway and the down regulate JAK/STAT pathway but some different biological pathway exist in estrogen negative cells where c-Myc is primarily controlled at the level of RNA stability [51-52]. In estrogen negative cells (SKBR-3), cucurbitacin B reduces the half life of the RNA and leading to the loss of activation of hTERT. Therefore, in both type cell line, cucurbitacin B could be acting via c-Myc, directly or indirectly, leading to the reduction of telomerase activity, suppressed the cellular proliferation, and blockage the cell cycle G2/M, induced the apoptosis pathway. Another signalling pathway by which, cucurbitacin B can inhibit the cellular growth of cancerous cells by inhibition of Wnt signaling pathway through reduction of Wnt-associated protein and reduced translocation of galectin-3-mediated β-catenin to the nucleus [53].

CONCLUSION

Cucurbitacin B from fruit of *C. indica* exerts a cellular growth inhibitory effect on breast cancer cells and cell lines (both estrogen positive and negative) but the most growth inhibition was seen in the ER negative breast cancer cell line SKBR-3. Cucurbitacin B, has been reported to exert the cytotoxicity on human breast cancer cell lines Even low concentrations of cucurbitacin B act as anticancer and anti proliferative effect overall breast cancer cells. During mechanism cucurbitacin B can directly reduce the expression of telomerase in the breast cancer cells, lead to down regulate the expression of various associated genes (hTERT and c-Myc) and blocks the cell cycle at G2/M, induced the apoptosis process. Cucurbitacin B induced apoptotic process in breast cancer cell and line that depend on the increased fraction of the subG0 phase of the cell cycle. In summary, anticancer and anti cellular proliferation activity of cucurbitacin B are revealed by inhibiting telomerase via down regulation of both hTERT and c-Myc expression in breast cancer cells.

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Conflict of interest statement

On the behalf of all authors, I hereby declare that there is no any potential conflict of interests among the authors and all authors have contributed efficiently in the submitted manuscript.

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