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## Vegetables that heal: The magic of red colour vegetables on breast cancer

K.P. Shamna\* and Muhammad Musthafa Poyil♦

Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia

\*Deseeya Ayurvedic Pharmaceuticals Ltd., Calicut-673 574, Kerala, India

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## Abstract

Globally, breast cancer is the leading cancer in the mammary gland of the female with high mortality rate, resulting serious health threat to public. The treatment of breast cancer options is crucial due to poor diagnosis and drug resistant to existing chemotherapeutic agents. The evidence-based analysis revealed the benefits of natural dietary foods such as vegetables for cancer prevention and treatment owing to its potential bioactive compounds which can reduce the cancer associated mortality. Exclusively, numerous bioactive compounds have distinct colour with different action in human body. Considering these facts, in this review, the anticancer properties of bioactive compounds such as lycopene,  $\beta$ -carotene, myricetin, betaine, quercetin, anthocyanin present in red coloured vegetables such as tomatoes, beetroot, red bell pepper and red onion against breast cancer cells and their mode of action have been investigated.

## 1. Introduction

Cancer is a collection of diseases which represents the unusual cell growth and spread in the human body and also produced severe physiological effects when it is left untreated. It remains a second leading cause of death globally, resulting serious threat to human health, creates severe economic burden in developed as well as developing countries owing to increased exposure of risk factors (Tan 2006; Pan American Health Organization, 2020). The cancer has occurred in any part of the tissue due to mutation in the normal cells creates the unsuitable environment which helps the cell neoplastic transformation (Gaikwad and Srivastava, 2021; Power and Robinson, 2006). Every year, more than millions of people were died owing to different types of cancer such as lung, breast, colon and prostate cancer. Among the others, breast cancer is the second leading cancer which represents 12% after the lung cancer in all populations, but it is the most important type of cancer which causes leading death globally in women's (Bray *et al.*, 2018). It becomes an important health issue in the population such as who are aged, non-communicable disease person and affected by other chronic diseases (Pisu *et al.*, 2017). Breast cancer is the most prevalent malignant tumor and also the rate of occurrence is increasing every year. The report says among eight women in the world, the one will get breast cancer due to various exogenous and endogenous risk factors including reproductive, genetic disorders, environmental factors and life style such as oral contraceptive use (Rieder *et al.*, 2016), early menarche (Bhadoria *et al.*, 2013), short term lactation (Ma *et al.*, 2017; Sisti *et al.*, 2016), alcohol consumption (Park *et al.*, 2014), night work (Jia *et al.*, 2013), diabetics (Charlot *et al.*, 2017; Park *et*

*al.*, 2017) and obesity (Pierobon *et al.*, 2013). Among them, the genetic disorder corresponds to only 10% of all breast cancers (Campeau *et al.*, 2008). The breast cancer is mainly an aggressive malignant tumor which is related to poor diagnosis and the survival rate is very minimal (Ferrini *et al.*, 2015; Castello *et al.*, 2015). The effective treatment option is the removal of breast followed by chemotherapy, hormone therapy and radiotherapy (Moulder and Hortobagyi, 2008). Unfortunately, the drug resistant and the undesirable side effects exhibited by current therapeutics limit the efficacy of the existing treatment option (Li *et al.*, 2017; Cazzaniga and Bonanni, 2012). Therefore, the prevention of breast cancer is more critical. Current scenario triggered the researchers to discover the alternative treatment options for breast cancer prevention and treatment with lower side effects. Therefore, in this review mainly focused on the role of bioactive compounds from red colour vegetables in breast cancer prevention and treatment.

Dietary natural food has gained much attention on prevention and treatment approach for breast cancer. There is a cluster of natural dietary foods are showed their protective effect on breast cancer prevention and treatment (Zhang *et al.*, 2016; Zheng *et al.*, 2016; Zhou *et al.*, 2016). The food and drug administration (FDA) and World health organisation's (WHO) have suggested that the regular intake of low fat content food, high fiber and consumption of vegetables and fruits along with some physical activity have decreases the overall cancer risks (Soerjomataram *et al.*, 2010; Turati *et al.*, 2015; Justo *et al.*, 2018). Besides, evidence from various epidemiological studies have highly recommended the consumption of vegetables, multigrains and fruits are reduced the breast cancer risk, recurrence and increase the survival rate (Farvid *et al.*, 2016; Grosso *et al.*, 2017). Particularly, some dietary foods are known for their dark colour pigments which accountable for anticancer bioactive compounds. Consequently, most of the plant based pigments from vegetables and fruits are notable by their prominent colours such as red, blue or purple, green, yellow and orange (Ahmad *et al.*, 2019;

Corresponding author: Dr. Muhammad Musthafa Poyil

Department of Basic Medical Sciences, College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, 11942, Saudi Arabia

E-mail: [pmusthu@gmail.com](mailto:pmusthu@gmail.com)

Tel.: +91-6565634412

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Khoo *et al.*, 2017; Chaudhary *et al.*, 2018; Lee *et al.*, 2017). Among them, red coloured fruits and vegetable are gaining much interest in the field of functional food science for the treatment of cancers owing to its specific bioactive compounds (Minich, 2019). Hence, in this review, we mainly focused on anti cancer activity of commonly used red coloured vegetables such as tomatoes, beetroot, red bell pepper, red onion, and their mechanism of action against breast cancer.

## 2. Anticancer activity of red coloured vegetables

### 2.1 Tomatoes

Tomatoes played a major role in balanced diet owing to its functional bioactive compounds such as lycopene, minerals, proteins, amino acids, potassium, polyphenols, flavonoids, carotenoids, *etc.* Considering the nutritional content, the tomato has been called as nutraceutical food due to their functional bioactive compounds which used to prevent the human diseases (Perveen *et al.*, 2015; Beynon *et al.*, 2019). The red colour of the ripen tomato due to the presence of carotenoid pigment called lycopene along with beta carotene which responsible for strong antioxidant potential and the ability for cancer prevention (Aghajanzpour *et al.*, 2017). Keeping this in mind, a study reported intake of tomato and their products reduced risk of cancer among other vegetables. For example, many reports are available for the association between colour and their anticancer property through various mechanism of action (Valderas-Martinez *et al.*, 2016). When, the regular intake of tomatoes reduced plasma concentration and the cell adhesion property which is most important for cancer cell invasion and metastasis process (Etminan *et al.*, 2004; Serrati *et al.*, 2020; Ohno *et al.*, 2020). Here, some important bioactive compounds from carotenoids such as lycopene, polyphenols and flavonoids were discussed for their anticancer property.

Many studies emphasized the health benefits of regular intake of tomato and their derived metabolites greatly reduced the risk of cancers. Among the other carotenoides, lycopene is frequently present in tomato which contains unsaturated hydrocarbon along with conjugated and unconjugated double chains responsible for red colouration and the most studied bioactive compounds present in tomato against various cell lines (Puah *et al.*, 2021; Madia *et al.*, 2021). Consequently, the regular lycopene supplement reduced the IGF 1 level thereby decrease in the high risk of breast cancer (Voskuil *et al.*, 2008; Grether-Beck *et al.*, 2017). Many studies suggested the lycopene anticancer property against breast cancer and highlighted the molecular mechanisms responsible for the effect of lycopene. Besides, the molecular mechanism of lycopene against various breast cancer cell lines such as HER2 positive SK-BR-3, triple negative MDA-MB-468 and ER/PR positive MCF 7 were investigated and the dose and time dependent activity was observed against the above-mentioned cell lines by cell cycle arrest at G0/G1 phase. The lycopene exhibited greatest activity against MDA-MB-468 by apoptosis and also induced the ERK1/2 activation along with suppression of cyclin D1. Consequently, lycopene inhibit the Akt phosphorylation followed by proapoptotic Bax upregulation (Takeshima *et al.*, 2014). In support of this, two studies were found the lycopene activity against breast cancer cell lines by suppression of anti apoptotic protein Bcl2 and up-of the proapoptotic protein BAX (Peng *et al.*, 2017). Likewise, lycopene antiproliferative activity was investigated against MCF7 breast cancer cell line at different concentration and the activity was achieved by targeting gap junction intercellular

communication and upregulation of connexin 43 expressions (Fornelli *et al.*, 2007). Similarly, Gloria *et al.* (2014) analysed the antiproliferative activity of lycopene against breast cancer cell lines MDA-MB-231 and 235 and MCF7 through cell proliferation inhibition, increased cell apoptosis and cell cycle arrest at several phases. The same way, Nahum *et al.* (2001) analysed the molecular mechanism of lycopene against various breast cancer cell lines including MCF7 and MCF7.7D1.13 and found the IGF mitogenic activity inhibition and cyclin D1 reduction in MCF7 cells. Consequently, lycopene showed the antiproliferative, anti invasive and antimetastatic property against breast cancer lines MDA-MB-231 and MCF 10 by reduced the Akt and ERK1/2 phosphorylation in MCF 10 revealed that these pathways played a major role in anticancer property of lycopene and also inhibited the cell migration, proliferation and invasion (Uppala *et al.*, 2013; Koh *et al.*, 2010). The lycopene can be used as a potential bioactive compound in the prevention and treatment of breast cancer due to its anticancer, anti-invasive, antimigrative and antiproliferative property with deciphered mode of action.

$\beta$ -carotene, is a second most important carotenoid with potent anticancer property responsible for red-orange colours present in tomatoes. Consequently, the  $\beta$ -carotene was evaluated for anticancer property against breast cancer cells and the activity was observed *via* blocking the AKT and ERK1/2 activation through signalling pathways and reduced the anti oxidant enzyme SOD 2 level by down-regulating the Nrf2 transactivation factor leading breast cancer cell death (Sowmya Shree *et al.*, 2017). Interestingly, report from meta-analysis with 19450 breast cancer patients suggested that, regular intake of  $\beta$ -carotene is significantly enhanced the survival rate of 30% increase in breast cancer patients (He *et al.*, 2018) and another study proved that higher concentration of  $\beta$ -carotene decreased the risk of breast cancer (Eliassen *et al.*, 2015). Consequently, the enhanced cytotoxicity of carotene was observed when it was conjugated with liposome against breast cancer cells (Gina *et al.*, 2022).

Myricetin from the group of flavonol is naturally found in tomatoes and their anticancer properties have been extensively studied (Barreto *et al.*, 2016). The anticancer activity of myricetin was studied against breast cancer cells and the compound was able to inhibit the angiogenesis through down regulating the signalling pathways of p38MAPK and VEGF/VEGFR2 (Zhou *et al.*, 2019). Similarly, in T47D breast cells, the myricetin induced cell death through apoptosis combined with increased apoptotic genes such as caspase 3, BAX/Bcl2 p53 expression (Soleimani *et al.*, 2020).

### 2.2 Red beet root

The red beet root is one of the most colourful vegetables which contains plenty of rich nutrients such as fat, carbohydrates, micro-nutrients and functional bioactive compounds including betanin, betaine, betatine, carotenoids, saponins, polyphenols, pectin and betalains which is soluble in water (Lim, 2016). The red beet root is known for its anticancer and anti-inflammatory properties. Consequently, the anticancer activity of beetroot enriched with betanin extract was investigated against breast cancer cells and the activity was mediated by apoptosis. The high concentration of betanin causes cell death through proliferation inhibition, cell cycle progression inhibition and also cyclin down regulation in breast cancer cells (Nowacki *et al.*, 2015). Similarly, betaine induced cell death in breast cancer cells *via* inhibition of alcohol induced transcription of

pol III, cell growth inhibition through down regulation of Brf1 and Pol III (Zhang *et al.*, 2013). Other bioactive compound beta vulgarin was able to inhibit the breast cancer cell growth, colony formation and also reduced the CD44+/CD24 count as well as inhibited the Stat3/S Stat 3/Sox 2 signalling pathways in breast cancer cells (Liu *et al.*, 2020). Another interesting study, the enhanced activity was observed when the red beet root extract was combined with doxorubicin against breast cancer cells *via* DNA intercalation mechanism (Kapadia *et al.*, 2011). In addition, another bioactive compound from red beet root as pectin induced the cytotoxicity on MCF 7 breast cancer cells (Concha *et al.*, 2013). The betaine had excellent anticancer activity in its higher concentration but the anticancer activity was increased when it was complexed with other potential compounds and showed synergism. Surprisingly, the enhanced activity of betaine was observed when it was complexed with *p*-SC4 and the activity was observed in various cells including breast cancer cells (Fahmy *et al.*, 2021).

### 2.3 Red bell peppers

The bell pepper is most popular vegetable globally due to their varied colour ranges such as green, yellow and red as well as flavour and nutritional value (Bae *et al.*, 2014). Among the other pepper, the red pepper gained more attention due to its high nutritional value and attractive colour. The red colour is due to the presence many carotenoids including  $\beta$ -carotene combined with pro vitamin, capsanthine and phenolic compounds such as luteolin, quercetin and capsaicinoids which are known for their anti oxidant and anticancer properties (Rao *et al.*, 2007). Among the others,  $\beta$ -carotene and quercetin played a major role in anticancer property of red bell pepper.

$\beta$ -carotene is the most important carotenoid present in red bell pepper which possess various biological properties including anticancer activity and reduce the cancer risk (Saini *et al.*, 2015; Pechinskii and Kuregyan, 2014). Consequently, the lycopene and  $\beta$ -carotene anti cancer property was evaluated against breast cancer cells. The cell viability was decreased after treatment with these carotenoids and the cell death was accomplished by increased cell apoptosis, inhibition of cell proliferation and cell cycle arrest at various cell stages. These findings suggested that carotenoids can be act as potential anti cancer agent against breast cancer cells (Gloria *et al.*, 2014). In support of this, a study reported the  $\beta$ -carotene mechanism of action on breast cancer cell by arresting the cell cycle and apoptosis.  $\beta$ -carotene regulated the genes responsible for oxidative stress by inhibiting akt and ERK  $\frac{1}{2}$  signalling pathways and also suppress the expression of Bcl-2 and NF-kB and cysteine aspartic proteases activation which induced the apoptosis in breast cancer cells (Shree *et al.*, 2017).

Quercetin is present in red pepper exhibited their anticancer properties against variety of cancers including breast cancer. Many epidemiological studies proved the anticancer activity of quercetin against breast cancer cells. Consequently, the quercetin can also overcome the side effect induced by cisplatin treatment. Surprisingly, the quercetin reduced the possible side effect induced by cisplatin such as kidney toxicity and also enhanced anti tumor activity was observed when it was combined with cisplatin against breast cancer induced *in vivo* mice model (Liu *et al.*, 2019). Numerous studies reported the plant derived quercetin mode of action such as activating the apoptotic pathways, cell cycle arrest, MMP-2 and MMP-9 pathway inhibition against breast cancer cells (Kashyap *et al.*, 2015).

Same way, quercetin induced the cell death of breast cancer cell by apoptosis through up regulating the caspase 3 and 8 expression and also induction of PARP cleavage in over expressing HER2 breast cancer cells (Seo *et al.*, 2016; Ranganathan *et al.*, 2015). Similarly, it can also inhibit the G2M phase in cell cycle of breast cancer cells after treatment (Choi *et al.*, 2001) and MMP-2 and MMP-9 (Lin *et al.*, 2008). In addition, the quercetin induced cell death *via* targeting other pathways including Akt/AMPK/mTOR in breast cancer cells (Rivera *et al.*, 2016; Jia *et al.*, 2018).

### 2.4 Red onion

Globally, onion is the most commonly used vegetable in cooking and also a good source for bioactive compounds (Ernivec *et al.*, 2021). Several studies have reported the presence of flavanols, phenols, tannins, anthocyanins, ferulic acid, vanillic acid and flavanoids which has anticancer properties (Albishi *et al.*, 2013; Ifesan, 2017; Yu *et al.*, 2021). An epidemiological study reported the correlation of high intake of red onion (*Allium cepa*) which reduces the risk of cancer effects and their potential anti cancer property (Challier *et al.*, 1998; Oancea *et al.*, 2020; Li *et al.*, 2017). Therefore, the ethanolic extract of red onion peel was investigated against breast cancer cell MDA-MB-231 resulting reduction in the cell proliferation and increased cell cycle arrest *via* phosphatidylinositol inhibition in breast cancer cell (Choe *et al.*, 2020). The report says more bioactive compounds were present in onion peel compared to flesh onion (Campone *et al.*, 2018) and it confer the therapeutic application in the treatment of various diseases such as cancer, cardiovascular diseases, obesity and microbial damage. Among the several bioactive compounds, quercetin and anthocyanin are played a major role in the therapeutic application in treating various diseases. Therefore, we focused the anti cancer properties of quercetin from red onion against breast cancer cells. The daily intake of quercetin reduces the tumor growth in breast cancer xenograft mice models (Wang *et al.*, 2014; Zhao *et al.*, 2016).

Consequently, numerous studies reported the *in vitro* and *in vivo* anti cancer activity of quercetin against breast cancer cells. But, the *in vitro* anticancer activity was mediated through prevention or inhibition of angiogenesis in breast cancer cells which resistant to tamoxifen while the *in vivo* activity was mediated by its antioxidant property (Oh *et al.*, 2010; Baghel *et al.*, 2012; Dajas *et al.*, 2012). The enhanced activity of quercetin was observed when combined with doxorubicin against breast cancer cells which was T cell specific resulting improvement in the immune response against the tumor growth (Du *et al.*, 2010). Here, it was noted that, due to its chemotherapeutic activity, quercetin is preventing several cancer cell type proliferations through exhibiting various mode of actions such as attachment to cell receptors, inhibiting the enzymes and signalling pathways which are responsible for activation of carcinogens leading a strong anti cancer molecule against various tumour cells (Rauf *et al.*, 2018; Gibellini *et al.*, 2011). Also, quercetin showed the anticancer activity against MDA-MB-231 and MCF 7 by promoting cell apoptosis, miR-146a expression regulation, mitochondrial pathways inhibition and activating caspase pathways (Tao *et al.*, 2015). Similarly, when the quercetin was used to treat the MCF 7 breast cancer cells, the activity was observed as dose and time dependent reduction in cell proliferation by Bax up-regulation and Bcl 2 down regulation (Duo *et al.*, 2012). Same way, quercetin also inhibits the insulin receptor signalling pathways and inhibiting the target genes which involved in EMT reversal in MDA-MB-231 breast cancer cells (Srinivasan *et al.*, 2016).

Anthocyanin is a water-soluble phenolic plant compound present in red onion and used as a dietary compound for various human diseases. Anthocyanin has exhibited their anticancer property against various cancer cell types by different mode of action. Consequently, the breast cancer cells exposed to anthocyanin, the activity was achieved by suppression of both mRNA and protein expression resulting inhibition in the cell cycle and VEGF signal pathways as well as miR-

124 expression induction leads to angiogenesis in breast cancer cells (Ma *et al.*, 2019). Similarly, the anthocyanin anticancer activity was evaluated *in vitro* and *in vivo* against HER 2 positive and trastuzumab resistant breast cancer cells and also able to inhibit the cell growth, migration and invasion, phosphorylation and induce apoptosis (Li *et al.*, 2016). The anti cancer activity of bioactive compounds from red colour vegetable against breast cancer cells and their mechanism of action are presented in Table 1.

**Table 1: Bioactive compounds anticancer activity against breast cancer cells**

Bioactive compounds	Red vegetables	Mechanism of action
Lycopene	Tomato	Cell cycle arrest, apoptosis, induced the ERK1/2 activation, suppression of cyclin D1, inhibition of Akt phosphorylation, Bax upregulation, IGF mitogenic activity inhibition
$\beta$ -carotene	Tomato, red bell pepper	AKT and ERK1/2 activation block, reduction in antioxidant enzyme SOD 2 level, down-regulation of Nrf 2 transactivation
Myricetin	Tomato	Angiogenesis Inhibition, apoptosis, down regulation of signalling pathways
Betaine, Betanin and Beta vulgaris	Beet root	Inhibition of alcohol induced transcription of pol III, cell growth inhibition, inhibition of cell growth, inhibition of signalling pathways, reduction in CD44+/CD24 count
Quercetin	Red bell pepper, red onion	Apoptosis, cell cycle arrest, induction of PARP cleavage, Bax up-regulation and Bcl 2 down regulation, miR-146a expression regulation, mitochondrial pathways inhibition and activating caspase pathways
Anthocyanin	Red onion	Cell cycle arrest, inhibition of VEGF signalling pathways, angiogenesis

### 3. Conclusion

The anticancer activity of most important bioactive compounds such as lycopene,  $\beta$ -carotene, myricetin, betaine, quercetin, anthocyanin present in red coloured vegetables such as tomatoes, beetroot, red bell pepper and red onion are studied against various breast cancer cells and the activity was mediated through diverse mechanism of action including cell growth inhibition, cell cycle arrest, inhibition of signalling pathways, suppression of migration and invasion and apoptosis. The bioactive compounds present in red coloured vegetables played a major role as dietary food supplements for various human diseases including cancers. Overall, these bioactive compounds derived from red coloured vegetables are most promising anti cancer bioactive molecules against breast cancer cells.

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### Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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