Commentary

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Flavonoids in Triple Negative Breast Cancer: Chemopreventive Phytonutrients

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Flavonoids are phytochemicals that found in a variety of fruits and vegetables and known to possess anti-oxidant, anti-inflammatory and anti-cancer properties [1,2]. It has been considered that flavonoids rich diet intake has promising role in human cancer prevention including breast cancer [3]. These phytonutrients have been traditionally used in Chinese and Ayurvedic medicine and are found to be associated with lower risk of breast cancer [4,5]. According to epidemiological studies, breast cancer is the most common malignancies in women around the globe [6]. Breast cancer has heterogeneous nature with each of its subtype shown distinct morphological and clinical behavior [7]. Several factors including genetic, epigenetic and transcriptomic alterations are proved to be responsible for this diverse nature of breast cancer [8]. Among other subtypes triple negative breast cancer (TNBC) is highly aggressive form of breast cancer [9]. Statically TNBC alone comprises of 10%-17% of all breast carcinomas with incidence rate of 6%-28% of breast cancer [10]. Although, TNBC accounts for small proportion of all breast cancers, but has high mortality rate due to its aggressive nature. TNBC is characterized by the absence of estrogen receptors (ERs), progesterone receptors (PRs) and human epidermal growth factor receptor 2 (HER2) with normal breast tissue–like, and basal-like phenotype [10]. Lack of ERs, PRs and HER2 in TNBC makes it more difficult to treat [11]. Currently used hormonal or targeted therapies are only effective against those tumors that has either overexpressed receptors or transcriptional factors. Since neither receptors nor HER2 overexpression is occurred in TNBC therefore the therapies are found to be ineffective [11]. Interestingly, several *in-vitro* experiments determined the risk reducing effect of flavonoids in TNBC and suggesting them as a promising therapy.

For example, Fisetin inhibited MDA-MB-468 and MDA-MB-231 cell's division and induced apoptosis involving mitochondrial membrane depolarization and activation of caspase-9 and caspase-8, as well as cleavage of PARP 1 [12]. Similarly, quercetin, another flavonoid compound also causees loss of membrane potential and activation of caspase cascade and PARP cleavage. *In-vitro* studies using MDA-MB-231 cells showed that exposure to quercetin leads to an enhanced expression of Bax and cyt c release from mitochondrial membrane [13]. Quercetin also induces apoptosis in MCF-7 and MDAMB-231 cell line through the suppression of Twist via p38MAPK signaling pathway [14]. Genistein inhibits the growth of MDA-MB-231 by regulating the apoptosis related genes and up-regulation of Bax and p21WAF1 molecular pathways [15]. Study also found that genistein induced apoptosis in MDA-MB-231 cells by down-regulating Bcl-2 and up-regulating Bax, cleavage of caspase-3 along with inhibition of NF-κB activity via the MEK5/ERK5 pathway [16]. Furthermore, data demonstrated that genistein inhibited the growth of MDA-MB-231 cells by inhibiting NF-κB activity via the Nocth-1 signaling pathway and down-regulated the expression of cyclin B1, Bcl-2 and Bcl-xL proteins [17].

Similarly, in other study, genistein also observed to inactivate NF-κB in MDA-MB-231 cells via Akt signaling pathway [18]. On the other hand, different studies determined G2/M phase arrest in MDA-MB-468 and MDA-MB-231 cells in response to fisetin and genistein treatments [12,19]. Results from another study suggesting that genistein-induced G2/M cell cycle arrest in MDA-MB-231 cells by modulating Ras/MAPK/AP-1 cancer signaling pathway [20]. Moreover, significant increase in connexin 43 (Cx43) levels was identified which in turn suppressed the invasion and metastatic of MDA-MB-231 after treatment with quercetin and genestein [21]. Furthermore, other member of flavonoids i.e. apigenin represses the HGF-induced cell migration and invasion in a dose-dependent manner via Akt phosphorylation and also inhibited integrin β4 function including cell–matrix adhesion and cell–endothelial cells adhesion in MDA-MB-231 cells [22].

In other study using MDA-MB-231 cells, isorhamnetin a flavonoid, was found to exert anti-metastatic effects by suppressing the expression and activity of MMP-2 and MMP-9 through inhibition of p38 MAPK and STAT3 signaling pathways [23]. Study using hesperetin treated MDA-MB-231 cells have investigated the impaired cell membrane translocation of GLUT4 and hence glucose transportation [24]. Therefore, flavonoids can exert significant anti-cancer functions through the regulation of crucial cancer signaling pathways and inclusion of flavonoid rich diet could be an effective approach to reduce the TNBC development risks.

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