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Synergetic actions of some commonly used phyto-chemicals augment cell cycle arrest actions in Cancer cells: A Review

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Abstract

Arresting the growth of the cells during the cell cycle is one of the main targets in cancer therapy. There are varied therapeutic chemicals to target the cancer cell growth available both in current as well as in alternative medicines from plant sources. Of the many plant polyphenols that have been studied and found to play a role in the cell cycle arrest, the most commonly used polyphenols from Turmeric (curcumin), Green Tea (EGCG) and ginger (6-gingerol) are studied extensively. All these three are reported to control cancer cell's proliferation by arresting the growth at different phases of the cell growth cycle. As they are targeting a common factor, the cell growth, by following a different or a similar molecular paths, it is expected that, their efficacy is likely to improve due to possible synergistic action when they are used together. Research findings that support this hypothesis are analyzed.

Key words: Plant polyphenols, cancer, cell cycle arrest, synergism.

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INTRODUCTION

Cancer is nothing but an unwanted and unregulated growth of a particular tissue that at one stage spread to other organs and block vital functions of the organs. One of the 'Hall mark' characters of the cancer cells is their capacity to proliferate constitutively. This is as a result of unregulated and continuous cell cycle. Therefore, scientists started searching solutions to check cancer growth by targeting cell cycle (Buolamwini , 2000; Owa *et al*., 2001; Schwartz and Shah, 2005; Meeran and Katiyar, 2008; Dickson and Schwartz, 2009; Gabrielli *et al*., 2012; Bhullar *et al.,* 2018). Some of the chemotherapy drugs developed for targeting the cell cycle are listed by Dickson and Schwartz, (2009) and recently by Christopher *et al.* (2018). Similarly, Meeran and Katiyar (2008) listed out many phyto-chemicals that have the capacity to arrest abnormal cell cycle in many cancer cell lines. Bhullar *et al*. (2018) in their recent review provides an overview of kinase-targeted (cell cycle arrest) drug discovery and development in relation to oncology and highlight the challenges and future potential for kinase-targeted cancer therapies. Since the development of the first protein kinase inhibitor, in the early 1980s, 37 kinase inhibitors have received FDA approval for treatment of malignancies such as breast and lung cancer. Furthermore, about 150 kinase-targeted drugs are in clinical phase trials, and many kinase-specific inhibitors are in the preclinical stage of drug development.

The cell cycle is the recurring sequence of events that results in cell division. The cell cycle has been divided into four phases: Gap phase 1 (G1); DNA synthesis (S); Gap phase 2 (G2), during which the cell prepares itself for division; and Mitosis (M) during which the chromosomes separate and the cell divides. All these four phases are controlled and regulated by sequential activation and inactivation of many "check points" that monitor the status of the cell as well as environmental cues (Roa and Johnson, 1970). Checkpoints are defined operationally as a gene product or subset of gene products that when mutated confer independence on a cellular process that was previously dependent upon completion of another cellular process (McDonald and El-Deiry, 2000). Regulation of these check-points ensures proper cell cycle that ultimately stops uncontrolled proliferation of the cells. In the process of regulated cell cycle, abnormal or muted cells are either made into normal or they are destroyed by a process called apoptosis. This ensures all cells produced as a result of cell division are non-cancerous normal cells. Cyclins and cyclin-dependent kinases (CDKs) are the key players involved in the cell cycle progression.

While the CDKs join with regulatory proteins called cyclins to drive the cell through the cycle, the

CDK inhibitor proteins (CDKIs) block specific interactions.

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Different members of the CDK family, in association with different cyclins, represent key switches at various points in the cell cycle. The involvements of various types of CDKs and cyclins in regulating the above said sequential phases, G1, S, G2 and M are described by Dickson and Schwartz (2009) and presented in Fig. 1

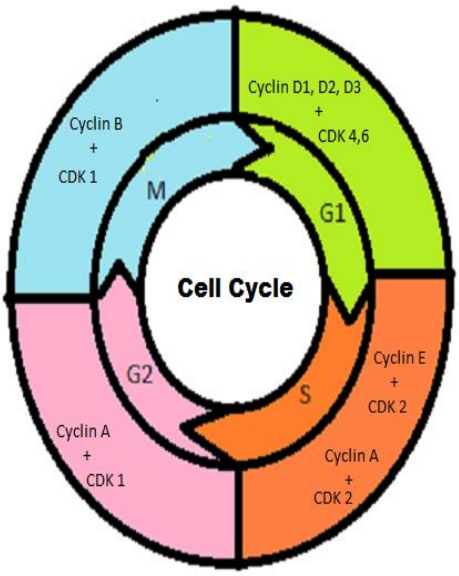

Fig. 1. Involvement of different cyclins and their kineses in different phases of the cell cycle (refer text).

For a cell to divide, the above said sequential chain of actions in various phases are to be completed. Any break or disturbances in any of the four phases, results in stoppage of cell division. Therefore, attacking a single activity, the cell cycle, has become a relatively more effective way to control cancer growth than targeting multiple molecular pathways. As this single activity occurs in different phases, attacking any one phase is as effective as attacking the activity as a whole. Further, targeting all phases at a stretch would be more effective therapeutic strategy as, if the target on one phase is missed or becomes ineffective, the other targets on other phases will take care of in the stoppage of the cycle. Therefore, simultaneous use of different cell cycle inhibitors of different phases would be the most appropriate therapeutic measure for achieving the highest results.

In the present review it is proposed to find out the therapeutic effects of some commonly used phyto-chemicals that have been studied extensively for their anti-cancer properties particularly their cell cycle arrest properties. They include Curcumin from turmeric, Catachins from green tea and Gingirol / shaogal from ginger. These three phyto-chemicals have been also known for their synergetic effects in attacking in various cancer lines. (Khafif *et al.,* 1998; Somers-Edgar *et al.,* 2008; Ahmad *et al.,* 1997 & 2011; Rao *et al.,* 2012; Beulaja *et al.,* 2012; Zhou et al., 2013). It is therefore, presumed that, while using all these phytochemicals together, their differential actions at different phases of cell arrest check points may reflect their synergism.

We will see here how these three phyto-chemicals act at different check points of different phases of the cell cycles of different cancer cell lines.

Actions of curcumin in cell cycle arrest

Among the four phases of the cell cycle, the curcumin is found to act more on the G2 / M phase arrest than the other phases (Chen *et al.,* 1999; Moragoda *et al.,* 2001; Park *et al.,* 2006; Liu *et al.,* 2007; Aggarwal *et al.,* 2007; Sahu *et al.,* 2009; Guo *et al.,* 2013; Berrak *et al.,* 2016, Hu *et al.,* 2017). However, G1 / S phase cell cycle arrest is also reported in a few cases (Shishodia *et al.,* 2005; Srivastava *et al.,* 2007; Aggarwal *et al.,* 2007). The molecular mechanisms involved in the above G2 / M cell cycle phase arrests although described variedly by the above authors, their findings reveal some common molecular mechanisms such as, suppression of the cyclins, B and A and their kineses (cdks) activities and activation of their inhibitor genes, p53 and p21 in the said G2 / M arrest (Fig. 2).

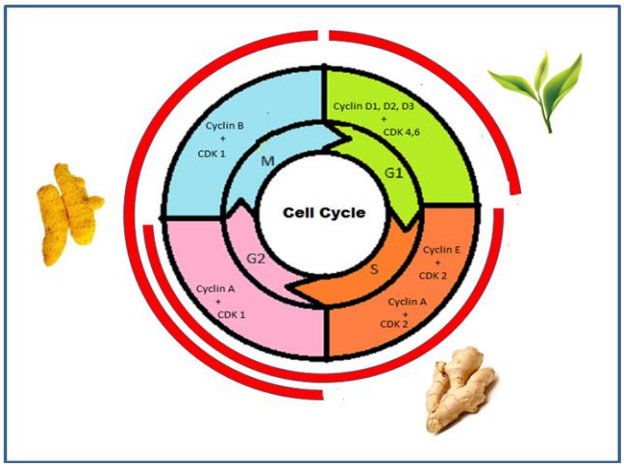

Fig. 2. Possible synergistic actions of polyphenols from Turmeric, Green tea and Ginger on different cell cycle regulators in cell cycle arrest. The actions of the green tea poliphenols are mostly restricted with G1 phaese. Whereas, the Ginger polyphenols act on both G1 / S and G2 phases. The actions of Turmeric polyphenol (curcumin) mostly seen in the late cell cycle phase G2 / M and overlaps the Ginger polyphenol actions in G2 phase.

Actions of Green tea polyphenols

Among the several polyphenols found in the Green tea, the molecular actions of the polyphenol EGCG is

extensively studied and reported in the cell cycle arrest mechanism. In contrast to the action of the Curcumin, the green tea is mainly involved in the first phase of the cell cycle, the G0/G1 (Liang *et al.,* 1999; Gupta *et al.,* 2003; Shankar *et al.,* 2007; Balasubramayam *et al.,* 2010; Nandakunar *et al.,* 2011; Thakur *et al.,* 2012). The main mechanism reported in their findings are, activation and upregulation of tumor suppressor genes, p53, p21, p16 followed by inactivation of cell cycle promoters, cyclin, D1 and E and their kinins, cdk, 2,4,6 (Fig.2).

Action of ginger polyphenols:

The actions of the ginger polyphenols in the cell cycle arrest seem to be intermediate between Curcumin and EGCG by acting both on G1/S and G2/M cell cycle phases (Fig. 2). There are reports saying that the 6-gingerol acts on both phases of cell cycle arrest in the same cancer line cells (Abdullah *et al.,* 2010 ; Kapoor *et al.,* 2016). The molecular mechanisms involved in G2/N phase cell cycle arrest are, the up regulations of cdk inhibitor proteins p21 & GADD45a and down regulation of cytokine kinases, cdc2 and cdc25A (Lin *et al.,* 2012; Qi *et al.,* 2015). The molecular mechanisms involved in G1/S arrest are, decrease in Cyclin A and cdk (Park *et al.,* 2006) and suppression of Cyclin D1 activity (Lee *et al.,* 2008) (Fig.2).

DISCUSSION

While reviewing the role of phytochemicals as cell cycle modulators, Singh *et al*. (2002) pointed out the importance of various phytochemicals in enhancing the cell cycle arrest mechanisms as a means of checking cancer growth. However, he has not reviewed the synergistic actions if any existing among those phytochemicals. In this present review the possibility of existence of synergistic actions is analyzed using the said three different phytochemicals. The actions of these three polyphenolic compounds in arresting the cell cycle in different phases and different molecular pathways in various cancer cell lines have been presented. Among these three, the Green tea molecule predominantly attack on the G1 phase while the ginger molecule mainly attacks the G2 phase of the cell cycle in cancer cells. Whereas, the cucumin has the capacity to attack equally both check points, that is, G1/S and G2/M (Fig. 2).

Although these polyphenolic compound attack cancer cell growth by checking the cell cycle arrest independently either by same means or different means, the efficiency may differ among themselves. In this connection it is believed that, the combinations of these compounds are likely to increase their efficiency by synergistic means. Such synergistic actions found between these compounds have already been reported in other anticancer actions. For example, synergism between curcumin and Green tea has been reported by various authors (Suganuma *et al.,* 2010; Saha *et al.,* 2010; Beulaja *et al.,* 2012; Khafif *et al.,* 1998; Zhou *et al.,* 2013; Somers-Edgar *et al.,* 2008). Similarly, synergistic actions of curcumin and ginger have been reported by Kurapati *et al.* (2012) and Roa *et al.* (2012). But, no report on the existence of synergism with reference to anticancer activity of the polyphenols from all the three (curcumin, green tea and ginger) is available. However, use of multiple herbal compounds is a common practice in the Indian and Chinese systems of medicine in order to improve their efficacy by synergistic means (Biavatti, 2009).

Possible synergism in the cell cycle molecular pathway

While studying the molecular pathway followed by these three herbal products in arresting the cell cycle, it is observed that, all the polyphenols, curcumim, EGCG and 6-gingerol, target the epigenetic protein molecule, p21. It is seen that although all the three are acting through p21 by enhancing its activity, the action of the p21 gene in the cell cycle arrest vary with the individual polyphenol depending upon the type of cancer cell lines (Fig. 3). While cucumin acts on p21 and arrests cell cycle both in G1/S and in G2/M phases by taking three different molecular pathways,

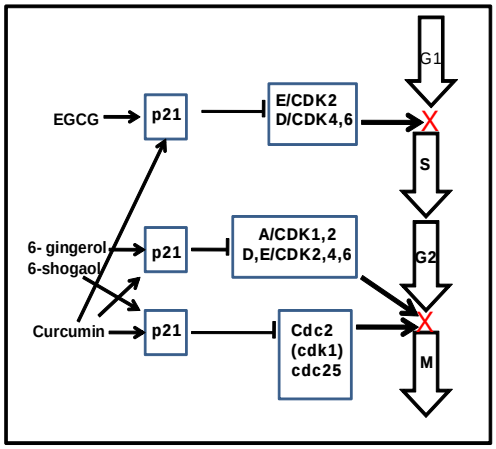

Fig. 3. Different molecular pathways on the activation of p21 epigenitic protein by different polyphenols. On activation of the p21 protein by curcumin, the molecular path ways in arresting the cell cycle vary with different cancer line cells (refer text). Activation by EGCG, the p21 controls a single path that results mostly in G1/S arrest. Similarly, ginger polyphenols participate in two molecular pathways by activating p21. If all the three plant food products are taken together for cancer control, it is expected that the efficacy of their combined actions will be maximized as a result of synergistic action.

the EGCG acts on p21 and arrest cell cycle at G1/S phase by following only one pathway. Whereas, the Ginger follow two pathways and arrests the cell cycle at G2/M phase by activation p21. Since all the three polyphenols act on the same gene but follow different molecular pathways, their efficacy in arresting the cell cycle are likely to be enhanced following synergistic principle. Moreover, every phase of the cell cycle is taken care of by these polyphenols either individually or jointly thereby, if any of the cells able to skip / escape from the target in G1 phase, they are likely to be caught either in S phase or G2 phase. This will ensure highest efficacy in the action of cell cycle arrest if all three are acting simultaneously together.

Of these several check points discussed above, it is said that the crucial check point that are responsible for the genesis and progression of cancer is the G1/S. That is being so, the role of EGCG and curcumin polyphenols in arresting this check point may be considered crucial. If synergic action exists between these two, that will contribute more in the control of genesis and progression of cancer. In this connection the work of Khafif *et al.* (1998) is worth mentioning. They studied the quantization of chemopreventive synergism between epigallocatechin-3-gallate (EGCG) and curcumin in normal, premalignant and malignant human oral epithelial cells. Their use of combinations was based on cell cycle results showing differential growth arrest. EGCG blocked cells in G1, whereas curcumin induced an S/G2M block. Based on differential mechanisms for growth inhibition, they hypothesized that combination treatment would be more effective than single agent since cells could be simultaneously blocked at multiple checkpoints. In support of their hypothesis, their study revealed that, the total cell arrest was the highest when the cells were treated with curcumin and EGCG together compared to their individual effects. They further concluded that such higher outcome could be achieved with relatively low concentration of the materials.

Coming to the possibility of existence of synergism in G2/M cell cycle arrest, it is stated already that both the ginger compound and curcumin have independent role in the said cell cycle arrest. However, a direct synergistic actions of these two with respect to cell cycle arrest in G2/M phase is not reported. However, the study of Roa *et al.* (2012) provide some useful information regarding existence of synergism between these two in controlling the cancer cell growth. In their study they reported the existence of synergism in the extracts of turmeric (curcuminoids) and Ginger (gingerol and shogoal) combination. They tested their toxicity on the prostate cancer lines by determining the growth rates of the cancer cells in a particular concentration with suitable control and normal cells. They found that both the extracts have toxic effect and prohibit cancer cell growth individually and, the effect of turmeric extract is comparatively higher than the ginger extract with similar concentration. They further found that with the same concentration of their combination, the effect was far higher than their individual effects combined together with similar concentration. However, the mechanism at molecular level involved in the growth control is not reported by them.

This review emphasizes the need for further study on the action of all the three polyphenolic compounds together in order to find out the quantum of increased efficacy as a result of synergism. Such study will pave way to the use of these three common dietary compounds as the most effective therapeutic agents against cancer.

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