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Review Article

Quercetin and Ursolic Acid: Dietary Moieties with Promising Role in Tumor Cell Cycle Arrest

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Abstract

Despite extensive efforts done in the recent decades, cancer has still remained an incurable disorder. On the other hand, there is no doubt that different natural compounds possess a huge potential to suppress the promotion and progression of tumorigenesis, and numerous studies have described the possible molecular mechanisms of such substances. Probably one of the most efficient ways to hinder the multiplication of cancer cells is to arrest their cell cycle progression. Therefore, in the current article, a detailed review is presented about the arrest of cell cycle in different phases followed by exposure of cancer cells to two natural dietary agents, quercetin, and ursolic acid. Both these compounds have previously been shown to exert anticancer properties, whereas pleiotropic action mechanisms were proposed. The current work describes a variety of molecules occupied in regulation of cell cycle progression and transition between different phases initiated by treatment of cancer cells with the respective flavonoid and triterpenoid. It is clear that better knowledge about the processes and molecules involved in cell cycle, as well as possibilities to modulate such mechanisms by natural compounds, may lead to the development of more efficient and targeted chemopreventive and chemotherapeutic strategies in the future.

Keywords: Cancer treatment and prevention; Cell cycle arrest; Natural dietary agents; Quercetin; Ursolic acid

Introduction

Studies in last few decades utilizing phytochemicals have ameliorated and emerged as an incipient platform for cancer treatment [1-3]. Several phytochemicals with anti-cancer properties have superseded the synthetic chemotherapeutic molecules due to lesser side effects [4]. Among the variety of health benign phytochemicals, quercetin (Quer, flavonoid) and ursolic acid (UA, triterpenoid) are emerging as promising therapeutics [5-15]. Being pharmacologically active, these phytochemicals are intensively utilized in chemoprevention and treatment. UA and Quer are kenned to modulate the sundry anti-cancer cell signaling pathways, such as induction of apoptosis, anti-angiogenesis, anti-metastasis, and cell cycle inhibition [16-20]. Especially in the cell cycle, a variety of different transcriptional factors and regulatory proteins are kenned to play a paramount role that is being targeted for cancer treatment and prevention.

In most eukaryotes, cell cycle-regulated transcription can be grouped into three main waves that coincide with the different transition points during the cell cycle, namely G1-to-S, G2-to-M and M-to-G1 [21,22]. Following mitotic division, a somatic cell undergoes an interim reposing phase called G0 phase which is followed by preparation of cell division through G1, S, and G2 phases which are further followed by next mitotic division [21,23] This cyclic order of physiological events comprising the mitotic division, reposing phase and preparation of cell division followed by next mitotic division is referred as the cell cycle. The transition from G0 to G1 phase of a cell cycle is tightly regulated by the balancing activity of positive signal engendered from mitogenic signals like magnification factors, hormones, amino acids and negative signals originated from Cyclin Inhibitory Proteins (CIPs) and Kinase Inhibitory Proteins (KIPs) [24,25]. At physiological state, positive signals subsist at their basal level and negative signals at their peak level in undivided somatic cells at G0 phase whereas the cells enter G1 phase only when negative signals minimize and positive signals reach their peak [26]. The length of the G0 phase varies from cell type to cell type. For example, while neuronal cells may have perennial G0 phase, the White Blood Cells (WBC) may have G0 phase for the only a couple of days. In contrast, cancer cells may have a very short span of G0 phase or none at all [26,27]. This designates that cancer cells are always in active cell cycle and cell division occurs perpetually irrespective of the presence of magnification promoting positive signals or absence of negative signals in the cellular environment. Mutation in the positive signaling molecules (e.g. magnification factor receptors) or negative signaling molecules (e.g P53) may be one of the vital reasons for this kind of uninterrupted, perpetual cell division of cancer cells [26,28].

Consequently, regulation of cell cycle is most paramount to regulate uncontrolled and aberrant proliferation of cancer cells. Quer and UA have been studied in sundry cancer cell lines and in *in-vivo* cancer models and declared as cell cycle inhibitors [29,30]. Up- and down-regulation of sundry cell cycle inhibitors and other regulatory proteins in the presence of these phytochemicals have been noted in various experiments. The present review summarizes the all known mechanisms of cell cycle inhibition by Quer and UA.

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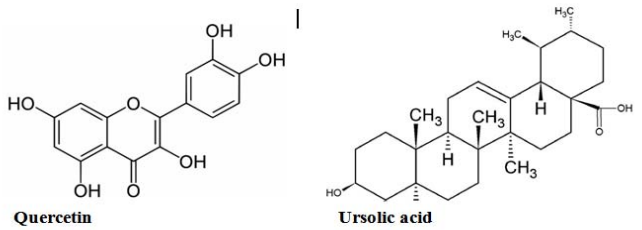

Figure 1: Chemical structure of quercetin and ursolic acid.

Chemistry of Quercetin and Ursolic Acid

Quer (3,5,7,3',4'–Penta hydroxy flavone) is a flavonol belonging to the class of polyphenolic flavonoids which is characterized by the presence of five hydroxyl groups on C_6-C_3-C_6 backbone structure especially a 3-OH group on the pyrone ring (ring C) [31]. It is the most important and abundant flavonol being found in apples, onions, and blueberries at a higher level while in form of glycoside [32-34]. It is synthesized by two methods: (i) By the cyclization of chalcone of 2,4-dimethoxy-6-hydroxyacetophenone and 3,4-dimethoxybenzaldehyde; (ii) The condensation of ω-Methoxyphloroacetophenone with a veratric anhydride in the presence of the potassium salt of 3,4-dimethoxybenzoic acid [35].

UA (3β-hydroxy-urs-12-en-28-oic acid) is a pentacyclic triterpenoid (C30) of ursane (α-amyrin) and it consists five cycles of six-membered rings with *trans* junction of rings like A/B, B/C, C/D and the cis junction of rings such as D/E. In this molecule, one hydroxyl group is attached at the C-3 position, one carboxylic group at C-17 and a double bond is present at C-12 while the seven methyl groups are linked at C-4, C-4, C-8, C-10, C-14 C-19 and C-20. The main sources of UA are reported to be berries and peels of fruits and its acetate derivative was synthesized from α-amyrinbenzoate [36,37] (Figure 1).

Mechanism of Cancer Cell Cycle Inhibition by Quercetin and Ursolic Acid

G0/G1 checkpoint regulation by quercetin and ursolic acid

In the cell cycle, G0 is the quiescent phase. The most non-proliferative cells of multicellular organism entering into this phase from G1 state and remain in it till no further stimuli come [21]. Signals in the form of DNA damage or degradation and presence of carcinogen stimulate the cell from the G0→G1 state. Next, G1 (magnification phase) is the first phase within interphase which is characterized by most biosynthetic activities including preparation of DNA replication to fortify precise cell division. The G0/G1 checkpoint is most tightly regulated by sundry proteins and transcriptional factors. In mammalian cells, the molecules including cyclins D and E form active protein kinase complexes with Cdk proteins (CDK4/CDK6, CDK2) and are required for progression of cells through G→S phase. Overexpression of cyclin D has been associated with sundry human cancers that push the cell from G to S phase [38-41]. The cyclin D/Cdk4, Cdk6 complexes function by phosphorylating the pRb protein [42,43] which in unphosphorylated state suppresses the G1→S progression [44]. Rb (retinoblastoma), a negative regulator of cell cycle, binds to and inhibits transcription factors of the E2F family, which are composed of dimers of an E2F protein and a Dimerization

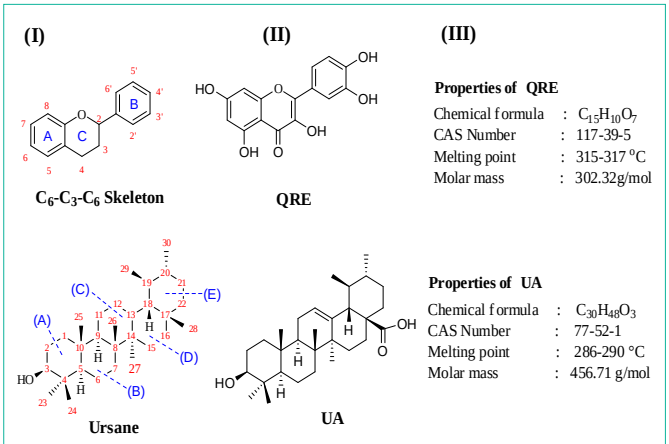

Figure 2: Chemistry of Quercetin and Ursolic acid.

Partner (DP) protein and control the G1→S phase [45,46]. pRb molecule additionally regulates the cyclin A and cdc2 expression and put these genes product under G1 cyclin control like cyclins D and E. Another cyclin/Cdk complex that play a crucial role in the G1/S phase transition is cyclin E/Cdk2. Most of the synthetic and natural anti-cancer agents target this checkpoint to contravene the cancer cell proliferation. Results suggest that flavonoids and triterpenoids exhibit consequential anti-tumor effects by suppressing cell proliferation, promoting apoptosis and inducing cell cycle arrest in both in-vitro and *in vivo* tumor models [47]. Cell cycle study of UA-treated HepG2 cell line explored the G0/G1 cell cycle arrest induction via up-regulation of p21 (WAF1) expression [29,48]. An in-vitro experiment utilizing HCT15 (human colon cancer cell line) cells found the more accumulation of cancer cells in G0/G1 phase after 36h treatment of UA [49]. Inhibition of MCF-7 breast cancer cells demonstrated the pro-apoptotic effect of UA with cyclin D1/CDK4 inactivation, which is kenned to play a crucial role in cell cycle progression [50]. Similarly, utilizing SNG-2 and HEC108 (endometrial adenocarcinoma cancer cell lines) cells, studies showed the cell cycle inhibitory effect of UA in G1 phase via modulating MAPK signaling pathways [51] (Figure 2).

Quer, a flavonoid molecule was also kenned to block cell cycle progression at G1 phase and exert its magnification inhibitory effect through the incrementation of Cdk inhibitors p21 and p27 and tumor suppressor p53 in HepG2 cells [52]. The down-regulation of cyclin D1 level linked to the G1/S phase alteration was found in Quer-treated human ovarian carcinoma and osteosarcoma cell lines [53]. In a homogeneous way, Quer mediated G1 cell cycle arrest by down-regulation of cyclin D1/Cdk4 and cyclin E/Cdk2 and up-regulation of p21 proteins in vascular smooth endothelial cells [54,55]. Again, it was found that Quer incremented the expression of Rb gene and subsequently arrested HK1 and CNE2 cells in G2/M or G0/G1 cell cycle phase (Ong et al. 2004). Further, the proliferation of ovarian cancer SKOV-3 cells and Malignant Mesothelioma (MM) MSTO-211H and H2452 cells has been inhibited by treatment of Quer which blocked cell cycle progression from G0/G1 to G2/M and also induced cell apoptosis [56,57]. Quer suppressed HSP27-mediated cyclin D1 expression and ergo obstructed the U937 leukemia cell proliferation in the G1 phase [58,59]. Withal, the reduction of cyclin D level was found in Quer-treated SKOV3 and U2OSPt cells which could be linked to G1/S phase alteration.

S-phase arrest by quercetin and ursolic acid

S-phase (synthesis phase) represents DNA replication occurring between G1 and G2 phases and responds the precise and consummate DNA replication of all chromosomes to obviate any genetic abnormalities. Several magnification-dependent Cyclin-Dependent Kinases (CDKs) are required to promote DNA replication and to initiate G1→S phase transition. Cyclin E which is engendered during cell division binds to CDK2, forming the cyclin E-CDK2 complex and pushes the cell from G1→S phase (G1/S, which initiates the G2/M transition) [60,61]. Recently, Wang and his colleagues found that the S-phase cell cycle arrest of GBC-SD and SGC-996 (gall bladder cancer cell lines) cells by UA was associated with mitochondrial apoptotic cell death [47].

Quer has also been proven a mediator of S-phase arrest [62]. The dose- and time-dependent inhibition of DNA synthesis and Thymidylate Synthase (TS), a key S-phase enzyme, has been associated with Quer exposure to SCC-9 cells, which thereafter arrested the cells in S phase [63]. Additionally, the arrest of MCF-7 cells in the S phase by down-regulation of Cdk2 and cyclins A and B and up-regulation of p53 and p57 proteins has also been found to be subjected to the Quer treatment [64,65].

G2/M checkpoint regulation by quercetin and ursolic acid

The G2/M DNA damage checkpoint is a consequential point that ascertains that only normal cell has to initiate the mitosis after proofreading [66]. Treatment of tumor cells with either flavonoid or triterpenoid or in combination enlightens the way of anti-tumor therapy that causes cell arrest in G2/M phase. Anti-cancer effect of Quer through the inhibition of the cell proliferation and an incremented arrest of the cells in G2/M phase was indeed described in an *in vitro* study [67]. Individually, as well as synergistically in combination with another chemotherapy drug, Quer induced G2/M arrest in the HT29 cells [68]. In adult male Wistar rats, the Quer-mediated arrest of cancer cells in the G2 phase with reduced expression of cyclin D1, cyclin A, cyclin B, and CDK1 has also been described [69]. Similarly, Quer elicited a spectacular extent of G2/M phase cell cycle arrest in HepG2 tumor cell line [70]. The reduction of cyclin D1 level that could be linked to the G1/S phase alteration has been found in Quer-treated human ovarian carcinoma and osteosarcoma cell lines [53]. Furthermore, results also demonstrated that Quer suppressed the viability of HeLa cells by inducing G2/M phase cell cycle arrest and mitochondrial apoptosis through a p53-dependent mechanism [71].

Regulation of other targets by quercetin and ursolic acid

Several regularity proteins other than cyclins and CDK indispensable during cell division are functionally vigorously organized in the mammalian cells [72-74]. Tumor suppressor protein/transcription factor p53 functions by binding to the regulatory sequences and trans-activating a number of genes, including p21, Mdm2, and GADD45 [75-78]. Another protein, p21, called also Cip1/Wafl, binds directly to cyclin-CDK2, -CDK1, and -CDK4/6 complexes and thus functions as a regulator of cell cycle progression at G1 and S phases [79,80]. The expression of p21 is tightly controlled by the tumor suppressor protein p53, through which this protein mediates the p53-dependent G1 phase arrest in replication to a variety of stress stimuli [81-83]. A study revealed that UA was able to inhibit Murine Double Minute-2 Protein (MDM2) and T-LAK Cell-Originated Protein Kinase (TOPK), the two negative regulators of p53, which in turn contributed to UA-induced p53 activation [84,85]. In addition, Quer-mediated up-regulation of p21, p27, p53, and Chk2, down-regulation of Cdk1 and cyclin B1, and phosphorylation of pRb followed by the arrest of the cell cycle in the G1 and G2/M phase have been found in a variety of cancer cell lines [52,86,87]. Furthermore, dose- and time-dependent treatment with Quer led to the arrest of MCF-7 breast cancer cells in the S phase as a result of the down-regulation of Cdk2 and cyclins A and B and the up-regulation of p53 and p57 [64,65]. The study done with HepG2 cells suggested that the anti-carcinogenic action of Quer was mediated by up-regulation of p53 and BAX and via down-regulation of Reactive Oxygen Species (ROS), PKC, P(I) 3K and COX [88,89]. Furthermore, Quer in combination with ellagic acid elevated the expression of p53 and p21 and MAP kinases, JNK1/2 and p38, in a more than additive manner, thus suggesting a synergistic mechanism of tumor inhibition [90] (Figure 3).

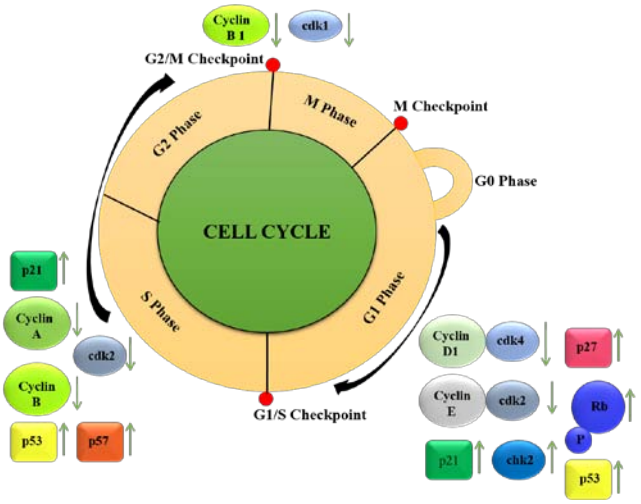

Figure 3: Mechanism of tumor cell cycle inhibition through modulation of several regulatory proteins under the influence of quer and UA (adopted from kashyap et. al. 2016-[91]).

Conclusion and Future Perspectives

The data presented above clearly show that the more insight into the function of all the regularity proteins of cell cycle could ensure the good treatment and better prognosis of cancer patients. Although most of the chemotherapeutic molecules are effective against the proliferation, development of resistance and use of alternative pathways biased their anti-proliferation effect [92,93]. The complete detail regarding all other targets of flavonoids and triterpenoids in tumor cell division is therefore urgently required to further extend their molecular mechanisms of cancer inhibition [1,47,91,94]. An organized up-regulation/down-regulation of several transcriptional factors or other regulatory proteins, cyclins, and cdks in the cancer cells is intentionally necessary to develop an effective way of treatment and prevention of malignant manifestations [41,95-97]. The targeted delivery of natural anti-cancer molecules with the help of nanoparticles might be used to design an ensured therapy for cancer prevention in future.

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