Anticancer Phytochemicals and Their Structure

Subjects: Oncology

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Cancer is a challenging disease and is the main cause of mortality worldwide; however, its impact is not evenly distributed. The cancer burden in developed and underdeveloped countries has increased over time owing to a variety of factors, including aging and growing populations, rapid socioeconomic growth, and changes in the incidence of risk factors. Since ancient times, plant-based medicines have been employed in clinical practice and have yielded good results. The modern research system and advanced screening techniques for plants' bioactive constituents have enabled phytochemical discovery for the prevention and treatment of challenging diseases such as cancer.

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1. Important Anticancer Phytochemicals from the Clinical Trials and Their Structure-Activity Relationship Data

According to a scientific report, phytochemicals may have substantial anticancer properties. Approximately 50% of the drugs approved between 1940 and 2014 were obtained directly or indirectly from natural sources [1]. Some important phytochemicals, currently in clinical trials, that showed good in vitro and in vivo potentials in different types of cancers are described below.

2. Curcumin

Curcumin, a lead phytochemical extracted from *Curcuma longa*, inhibits the growth of human glioma cells by inhibiting numerous cellular and nuclear factors. Curcumin increases the expression of various genes and their products, including p16, p21, and p53, Bax, EIK-1, Erk, c-Jun N-terminal kinase, early growth response protein 1, and caspases-3, -8, and -9, while reducing the expression of Bcl-2, pRB, cyclin D1, mTOR, NF-κB, and p65 [2].

The potent antioxidant property of curcumin is responsible for many of its medicinal actions, including its anticancer activity. The majority of natural antioxidative chemicals are either phenolic or -diketone compounds. But curcumin is one of the few antioxidative compounds that have both phenolic hydroxy and -diketone groups in a single molecule [3].

In one study, researchers investigated the importance of the phenolic hydroxy groups, and other substituents in the phenyl rings of curcumin and its analogs, to their antioxidant activities by using the three antioxidant bioassays (free radical scavenging activity by the ABTS method, free radical scavenging activity by the DPPH method, and inhibition of lipid peroxidation). In all the three assays, the phenolic curcumin analogs were more potent than the non-phenolic analogs, indicating that the phenolic groups are critical for antioxidant action. Curcumin is thought to be a classic phenolic chain-breaking antioxidant, donating H atoms from phenolic groups [4][5].

In another research study, curcumin analogs were synthesized or isolated from natural sources and evaluated for AR inhibitory activity in prostate cancer cell lines. Among these analogs, few exhibited the greatest inhibitory activity against the transcription of AR, while others showed less or no activity. Based on the bioassay results, researchers showed the SAR of curcumin analogs as anti-AR reagents as follows. (1) The conjugated β-diketone moiety is required for the activity. Saturating or removing the C=C bonds resulted in a decrease or loss of activity, while converting the β-diketone moiety to pyrazole leads to a reduction or loss of activity. (2) When the methylene group in the linker was not substituted, the inhibitory activity was significantly increased by substituting the phenolic hydroxy groups with methoxy or methoxycarbonylmethoxy groups. (3) Adding an ethoxycarbonylethyl group to the central methylene group dramatically improved the anti-AR action of curcumin when the phenyl ring substitution was retained. (4) Anti-AR activity was lost in all electron-withdrawing substitutions in the phenyl rings. The exact mechanism through which curcumin analogs block AR transcription is undisclosed [6][7][8][9]. Further initiatives need to be taken to extend the SAR and enhance anti-AR activities of curcumin.

3. Epigallocatechin Gallate (EGCG)

EGCG is the chief constituent of green tea that can restore the expression of tumor suppressor genes such as retinoid X receptor-alpha in breast cancer, ultimately preventing breast cancer by binding to other high-affinity proteins such as Zap-70 [10]. EGCG is also found to be effective against lung, colon, and prostate cancers by inducing DNA damage and AMPK signaling and inhibiting Notch1, MMP-2/9, and β-catenin expression [11][12][13].

In EGCG structure, the three aromatic rings are connected by a pyran ring. The structure of EGCG is thought to be responsible for its health-promoting properties. The potent antioxidant effect of catechins is achieved through quinone and semiquinone synthesis, which involves oxidation of phenolic groups with atomic or single electron transfer in the periphery aromatic rings [14][15]. These rings have been linked to a decrease in proteasome activity. Protected analogues are the only ones that suppress proteasome activity. In vitro, dehydroxylation of either one or both periphery aromatic rings inhibits proteasome inhibitory activity. Furthermore, apoptotic cell death is induced by these protected analogues in tumor cell-specific manure. These findings showed that the periphery aromatic rings peracetate protected EGCG analogues, have a lot of potential as anti-cancer and cancer-prevention drugs [16]. The first structure-activity correlations between EGCG and heat-shock protein 90 were described and analyzed by Khandelwal et al. His findings suggest that phenolic groups on the aromatic ring, adjacent to the pyrin ring, are useful in inhibiting heat-shock protein 90, whereas phenolic substituents on the faraway periphery ring are unfavorable [17]. Finally, when compared to catechins without the 5′-hydroxyl group, the hydroxyl group at the 5′-position in the upper aromatic ring inhibited urease up to 100-fold and also prevented Helicobacter pylori growth in the gut [18].

4. Genistein

Genistein, a potent anticancer compound, can be isolated from soybeans, lentils, chickpeas, and beans. It exhibits a pro-apoptotic effect in colon cancer and has a variety of functions: it upregulates Bax and p21, blocks topoisomerase II and NF-κB, and increases the expression of antioxidant enzymes such as glutathione peroxidase [19].

Genistein is a natural flavonoid that has been found to interact with several biological targets. After oral administration, its quick breakdown into inactive metabolites and rapid excretion from the body, are the main disadvantages of using genistein as a chemotherapeutic agent [20]. Therefore, to obtain better bioavailability compounds than genistein, a delayed compound metabolism is required. In one study, it was found that the proportion of metabolites was affected by the nature of the glycosidic bond. The metabolization of genistein derivatives with a more stable C-glycosidic bond was slower than derivatives with an O-glycosidic bond. It was also reported that linking a sugar moiety to the genistein structure increases its metabolism time in the body [21].

In another research work, it has been found that in comparison to the genistein parent molecule, novel genistein glycosyl derivatives with an O-glycosidic or C-glycosidic linkage have better antiproliferative effects. [22][23]. The C-7 or C-4′-hydroxyalkyl ethers of genistein (intermediates in the glycoconjugates synthesis), are found to be more active in preventing tumor cell growth than genistein. Furthermore, biological investigations have also revealed that derivatives with a substituent at the C-7 position inhibit the cell cycle in the G2 phase, whereas derivatives with a substituent at the C-4′ position disrupt the cell cycle in the G1 phase. [22]. It is concluded that the structural modification (hydroxyl group etherification) of genistein, successfully improved its antiproliferative activity.

5. Lycopene

Lycopene is a vibrant red pigment found in tomatoes, red carrots, watermelons, and red papaya. It plays a key role in targeting the PI3K/Akt pathway in stomach and pancreatic cancers by suppressing the expression of Bcl-2, an Erk protein. In breast, endometrial, prostate, and colon cancers, lycopene upregulates antioxidant enzymes GSH, GPxn, and GST and eliminates oxidative injury induced by toxins. Lycopene has been demonstrated to affect the growth and progression of HT-29 cells in culture and tumors in animal models by interfering with numerous cellular signal transduction pathways such as those of JNK and NF-κB. Lycopene also prevents infiltration, metastasis, and multiplication of human SW480 colon cancer cells by inhibiting JNK and NF-κB activation and suppressing the production of COX-2, IL-1, IL-6, IL-10, and iNOS [24][25].

Carotenoids promoted the expression of phase II enzymes by activating the electrophile/antioxidant response element (EpRE/ARE) transcription pathway. Phase II detoxifying enzymes is a key biological method for minimizing cancer risk. By disrupting the inhibitory effect of Keap1 on Nrf2, the key EpRE/ARE activating transcription factor; certain electrophilic phytonutrients have been demonstrated to stimulate the EpRE/ARE system. However, carotenoids like lycopene are

hydrophobic, lacking an electrophilic group, which is unlikely to activate Nrf2 and the EpRE/ARE system directly. The active mediators in lycopene's activation of the EpRE/ARE system are carotenoid oxidation products. Researchers discovered the main structure-activity rules for EpRE/ARE activation using a series of described mono- and di-apocarotenoids that might potentially be produced from in vivo metabolism of carotenoids (lycopene). Such active molecules are the aldehydes, not acids; the methyl group on the terminal aldehyde, which regulates the reactivity of the conjugated double bond, is responsible for the activity, and the main chain of the molecule is constituted of the dialdehyde's optimum length (12 carbons). The apocarotenals suppressed breast and prostate cancer cell proliferation with an efficacy comparable to that of EpRE/ARE activation. These findings may provide a molecular explanation for the cancer-preventive properties of carotenoids like lycopene [26][27].

6. Resveratrol

Resveratrol, a naturally occurring polyphenol, is found in peanuts, mulberries, grapes, blueberries, and bilberries. It plays a significant role in the treatment of different types of cancers, including colorectal, breast, pancreatic, liver, lung, and prostate cancers, by increasing the expression of Bax and p53 and decreasing the expression of NF-κB, AP-1, Bcl-2, MMPs, cyclins, COX-2, cyclin-dependent kinases, and cytokines. Resveratrol has been recognized to impede angiogenesis and suppress VEGF by decreasing MAP kinase phosphorylation [19].

A research study was carried out to find the structure-activity relationship of resveratrol in cancer. It was observed that the number and position of free phenolic hydroxyl groups have a key role in the anticancer activities of resveratrol. For this purpose, the researchers used different analogs of resveratrol having different phenolic hydroxyl groups for their anticancer activities in T24 cells. They found that the oxyresveratrol (3-OH glycosylated RV, having an extra -OH group than RV) has a greater inhibitory effect than RV but polydatin (3-OH glycosylated RV, lack of one -OH group) has a lesser effect than RV. This showed that the increased number of phenolic hydroxyl groups is responsible for the anticancer activity of RV []. Herath et al. proved the theory by discovering that when the hydroxyl groups in RV were replaced, the drug's pharmacological activity decreased [28]. Furthermore, Miksits et al. found that all of RV's sulfated metabolites were less effective against various cancer cell lines [29]. This suggests that the anti-tumor efficacy of RV can be affected by the conjugation of phenolic hydroxyl groups with sulfuric acid. Hence, again it is proved that the free phenolic hydroxyl groups are important for the antitumor effect of RV.

Currently, several investigations on plant-based drugs to treat cancer are ongoing. Some well-known and effective phytochemicals, such as vincristine, were approved by the FDA in 1963 to treat acute leukemia (brand name, Oncovin). Furthermore, paclitaxel was approved for the treatment of metastatic breast cancer, advanced lung cancer, and pancreatic cancer in 2005, 2012, and 2013, respectively, under the brand name, Abraxane. Curcumin, lycopene, and capsaicin, which are under Phase-III trials for prostate and breast cancers, are promising candidates for cancer therapy. Quercetin, genistein, silibinin, and EGCG are undergoing clinical trials or treatment for various types of cancers.

This research of anticancer plant-derived phytochemicals will help ethnomedicine and ethnopharmacology investigations, resulting in better outcomes for the medical potential of natural resources. Various phytochemicals highlighted in this research could be further investigated in clinical trials, enabling the availability of more effective anticancer medicines with fewer adverse effects.

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