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Molecular Targets of Dietary Phytochemicals for Human Chronic Diseases: Cancer, Obesity, and Alzheimer's Diseases

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ABSTRACT

Naturally occurring dietary phytochemicals have been recognized as possessing many health-promoting effects. Recent studies suggest that inflammation is closely related to chronic disease, including cancer, atherosclerosis, neurodegeneration, obesity, diabetes, asthma, articular rheumatism, and skin-aging. Extracellular stimuli transmit signals into a cell by activating the target kinases involved in inflammation and the onset of chronic diseases. Phytochemicals can directly bind to specific proteins involved in intracellular signaling networks and regulate their activity, leading to diverse physiological effects. A better understanding of the direct interactions between phytochemicals and target proteins would contribute to development of nutritional strategies for preventing or delaying the development of chronic diseases. In this review, recently identified molecular targets and signaling pathways regulated by phytochemicals will be discussed.

Key words: phytochemicals, molecular targets, carcinogenesis, adipogenesis, Alzheimer's disease

INTRODUCTION

Phytochemicals, widely known as the most common antioxidants in fruits and vegetables, have been proposed as primary chemopreventive agents. Polyphenols, the major group of phytochemicals, are characterized by the presence of more than one phenol unit or building block per molecule(1).

Uncontrolled inflammation often results in chronic diseases such as arthritis, autoimmune disorders, cancer, obesity, diabetes, and neurodegenerative and vascular disease(2). Multiple lines of inquiry have suggested that the health benefits of phytochemicals come from their anti-oxidant effects. However, the antioxidant properties of phytochemicals cannot explain all of their effects, such as specific inhibition of signal transduction and low effective dose. Numerous studies have reported that phytochemicals modulate various molecular signal transduction pathways, and research efforts have focused on the effects of phytochemicals on signaling cascades. However, the specific cellular and molecular targets of phytochemicals remain to be identified.

After the success of tamoxifen and finasteride, which have specific molecular targets, the development of recent cancer preventive agents has been based on the discovery of precise molecular targets(3). Targeting several signaling pathways simultaneously using phytochemicals to achieve synergistic effects in cancer treatment has been investigated, but the efficacy of this concept for obesity or neurodegenerative diseases has not been as rigorously explored. This review focuses on recent studies of molecular targets of natural phytochemicals in cancer, obesity, and Alzheimer's disease.

IMPORTANCE OF PHYTOCHEMICALS FOR CANCER, OBESITY, AND ALZHEIMER'S DISEASES

I. *Signaling Pathways and Potential Molecular Targets for Phytochemicals in Carcinogenesis*

Despite an enormous amount of research and rapid developments, cancer is still a leading cause of death worldwide. The lack of a 'magic bullet' has led to increased interest in chemoprevention as an alternative approach to the control of cancer. Epidemiological studies have shown that diets rich in polyphenols are associated with a lower risk of cancer developments(4,5). On this basis, attention has focused on dietary phytochemicals as an effective intervention in cancer development.

Chemoprevention is defined as a pharmacological approach used to arrest or reverse cancer development before invasion and metastasis occur(6). Chemotherapy of earlier stages of cancer, before invasion, has been relatively more successful. Therefore, researchers already

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possess the means to suppress cancer in its early, premalignant stages, before invasion and metastatic malignancy. An approach to cancer suppression that prevents carcinogenesis in its early stages is a logical, and perhaps the best, strategy to reduce the overall cancer risk.

There are various signaling pathways involved in inflammation. NF-κB and COX-2 are the major molecules that mediate inflammation[7]. Interactions of prostaglandins with their receptors to enhance cellular survival or stimulate angiogenesis have been proposed as the molecular mechanisms underlying the pro-carcinogenic roles of COX-2. LPS and TNF-α are the best studied inducers of COX-2[8].

Extracellular stimuli can activate numerous membrane receptors, such as EGFR, which convert these stimuli into various intracellular signals through activation of Src family kinases (SFK). Once activated, SFK transmits signals to various pathways[9]. SFK expression and activity are related to the development of malignancy in various human cancers. Previous studies have indicated that SFKs are associated with the activation of MAPKs, PI3K, and NF-κB signaling pathways. SFKs are, therefore, considered to be good targets for therapy[10,11].

II. *Processes and Potential Molecular Targets for Phytochemicals in Adipogenesis*

Obesity is a risk factor for diseases like diabetes, atherosclerosis, and certain cancers. Adipose mass can be decreased by reducing adipocytes, and adipogenesis is related to adipocyte differentiation and maturation. Although apoptosis of adipocytes is one strategy to treat obesity, it has the potential for side-effects. Moreover, there is space remaining after apoptosis of a large adipocyte, which new small adipocytes will fill. Because adipogenesis represents the early stage of fat formation, inhibition of adipogenesis pathways may be effective for treating obesity.

The first feature of the adipogenesis process is an alteration in cell shape paralleled by changes in the type and expression levels of extracellular matrix and cytoskeletal components[12]. These events further promote the expression of adipogenic transcription factors, including the central transcriptional regulators of adipogenesis, C/EBPα and PPAR γ. AMP-activated protein kinase (AMPK) is another target molecule for antiobesity treatments, since its activation inhibits adipogenesis differentiation.

III. *Processes and Potential Molecular Targets for Phytochemicals in Alzheimer's Disease (AD)*

Alzheimer's disease (AD) is an age-related neurodegenerative disease increasingly recognized as one of the most important medical problems affecting the elderly. Amyloid-β (Aβ) plays a critical role in the neuronal and synaptic degeneration of the brain regions implicated in learning and memory. The amyloid hypothesis suggests that abnormal proteolytic cleavage of amyloid precursor protein (APP) by β- and γ-secretase leads to excessive extracellular accumulation of Aβ in the AD brain[13]. Excessive Aβ aggregation might directly interact with neuronal membranes or indirectly stimulate diverse signaling pathways to impair neuronal synapses and dendrites, and cause local oxidative stress reactions and sustained inflammatory responses[14]. New approaches for preventing and treating AD have emphasized strategies to reduce the pathogenesis of Aβ.

The central nervous system is rich in polyunsaturated fatty acids and has a high content of transition metals and ascorbate, which together act as potent pro-oxidants[15]. Reactive oxygen species (ROS) and reactive nitrogen species cause injury to the brains of AD patients during the early development of the disease. Importantly, oxidative stress has been shown to precede the formation of senile plaques in the brain, the neuropatholgical hallmark of AD[16]. Markers of oxidative stress have been observed in the brains of AD patients. Thus, antioxidant enzymes and antioxidants have been demonstrated to protect against Aβ-induced cytotoxicity.

Recent studies suggest that inflammation may be one of the major contributors to the progression and chronicity of AD[17]. Fibrillar Aβ can bind to the complement factor C1 and potentially activate the classical complement pathway, which plays an important role in local recruitment and activation of microglia. Aβ can activate microglia directly by binding to the lipopolysaccharide (LPS) receptor CD14 or other scavenger receptors. Activated microglia induce the release of large amounts of pro-inflammatory mediators[17]. The potentially significant contribution of inflammatory mechanisms to the progression and chronicity of AD has prompted consideration of anti-inflammatory treatment strategies.

SELECTED DIETARY PHYTOCHEMICALS FOR PREVENTION OF CARCINOGENESIS, ADIPOGENESIS, AND AD

I. *Anticarcinogenic Agents*

Many researchers have attempted to identify novel polyphenols that have chemopreventive effects by targeting various oncogenic pathways. We will discuss the effects of representative examples that reversibly inhibit various carcinogenic pathways.

Resveratol, cyanidin and delphinidin are well-known polyphenols in red wine, grapes, and berries, which act as direct signaling regulators in carcinogenesis. COX-2 and LTA_4H are the molecular targets of resveratrol for the inhibition of colon and pancreatic cancer proliferation. Cyanidin suppresses COX-2 expression by directly targeting Raf, MKK4, and MEK1. Delphinidin attenuates COX-2 expression and neoplastic transformation. Molecular targets of delphinidin include Fyn, Raf, MEK1, ERKs, MKK4, and PI3K[3].

Various isoflavones in soybean and their metabolites, such as genistein, 7,3′ ,4′ - trihydroxy- isoflavone (7,3′ ,4′ -THIF) and equol, also inhibit diverse signaling pathways. Genistein suppresses EGFR kinase activity in A431 cells. Equol and 7,3',4'-THIF, metabolites of daidzein, inhibit neoplastic cell transformation by targeting MEK1 and PI3K, respectively, in JB6 P+ cells[9].

5-deoxykaempferol (5-DK), kaempferol, quercetin, and myricetin are flavonols, and directly inhibit multiple protein kinases involved in the signaling cascades in carcinogenesis. 5-DK has a chemopreventive effect on UVB-induced COX-2 and VEGF expression by targeting Src, PI3K, and RSK *in vitro* and *in vivo*. Keampferol exerts a strong protective effect against UVB-induced skin carcinogenesis by targeting Src. RSK and PI3K are also direct targets of Keampferol in cell proliferation and neoplastic transformation. Quercetin inhibits COX-2 expression and cell transformation by targeting PI3K and Raf, respectively, in JB6 P+ cells. Myricetin is a multi-target agent that inhibits skin carcinogenesis, metastatic phenotypes, and cell transformation by targeting Fyn, Raf, MKK4, MEK1, JAK1, and PI3K[9].

In general, synthetic cancer drugs target one protein because they have a high specificity, and that specificity causes side-effects, including high toxicity and drug resistance[3]. However, dietary phytochemicals are very effective for overcoming this difficulty because of their low toxicity and multi-target signal inhibition.

II. *Anti-Adipogenic Agents*

Phytochemicals have the potential to inhibit differentiation of pre-adipocytes, stimulate lipolysis, and induce apoptosis of existing adipocytes, thereby reducing the amount of adipose tissue. Several polyphenolic phytochemicals target the adipocyte life cycle. Inhibition of adipocyte differentiation is likely to be the safest and most effective strategy.

A number of studies have demonstrated that natural compounds, such as EGCG, genistein, resveratrol, CLA, capsaicin, and procyanidins, inhibit adipogenesis. The protein expression of PPAR and C/EBP was decreased in adipocytes treated with capsaicin, genistein, and EGCG. The decrease in adipogenesis caused by resveratrol was associated with increased expression of Sirt1, which promotes fat mobilization by repressing PPARγ. Genistein, EGCG and capsaicin inhibit adipocyte differentiation by activating AMPK[18].

Some studies indicated that synergistic effects on adipocytes could be achieved by using lower doses of two or more compounds, thereby decreasing potential toxic effects[19]. In order to develop an effective mixed treatment, target-based studies of natural anti-obesity agents are needed.

III. *Anti-AD Agents*

Epidemiological studies have suggested a positive relationship between consumption of curcumin, green tea catechins and prevention of AD[20]. Curcumin, the active component of the turmeric *Curcuma longa*, exerts anti-oxidant and anti-inflammatory effects. Its use has been proposed in the therapy of neurodegenerative disorders. Curcumin blocks the formation of Aβ fibrils. Although the precise anti-amyloidogenic mechanism of curcumin is unclear, it has been suggested that curcumin might be capable of specifically binding free Aβ and subsequently inhibiting polymerization of Aβ into Aβ fibrils. Curcumin also inhibits Aβ-induced cytokines and chemokines by suppressing lipoxygenase, COX-2, and NF-κB activation. Curcumin exhibits a strong antioxidant effect, and exerts its preventive effect by inducing expression of the antioxidant enzyme, heme oxygenase-1 (HO-1), and glutathione S-transferase[21,22].

Green tea catechins have been reported to activate MAPKs, protein kinase C, antioxidant enzymes and survival genes, and to control calcium homeostasis and APP processing. EGCG, a major polyphenolic catechin in green tea, reduced Aβ generation and plaques *in vitro* and *in vivo* by activating α-secretase activity and reducing that of β-secretase. EGCG attenuates preformation or formation of Aβ fibrils by directly binding to the native unfolded Aβ. EGCG also decreases malondialdehyde levels and caspase activity, protecting against Aβ-induced apoptosis and enhancing hippocampal neuronal survival [21,23].

Many researchers have demonstrated the inhibitory effect of dietary phytochemicals on neurodegeneration *in vitro* and *in vivo*. However, studies aiming to elucidate the targets of phytochemicals effective against AD have thus far been insufficient. Discovery of the molecular targets of polyphenolic natural compounds will provide an effective and safe solution to the problem of preventing Alzheimer's disease.

CONCLUSIONS

Using a combination of agents or a multi-targeted approach provides synergistic or additive preventive effects with the lowest active dose of each agent and so lowers the risk of adverse side effects. There is a trend towards personalized treatment as a requirement for effective human disease therapy, especially cancer. Conversely, a personalized diet for prevention of human chronic diseases has not been as well-documented, although prescribing a personalized diet for chronic diseases might make sense. In order to achieve this, it is first necessary to elucidate the precise molecular targets of phytochemicals.

Although there have been many reports of the benefits and targets of phytochemicals, these have relied mainly on cell and animal models. In order to apply phytochemicals as personalized preventive agents, their effects on humans must be assessed in clinical trials. In the future, personalized prevention methods using phytochemicals may have a crucial role in human disease. Rigorous research aiming to identify molecular targets, and conducting human studies with phytochemicals, would provide an effective approach to

personalized treatment and diet.

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