IJP (2017), Vol. 4, Issue 8 **(Review Article)**

Received on 17 March 2017; received in revised form, 23 May 2017; accepted, 30 May 2017; published 01 August 2017

REVIEW STUDY ON ROLE OF NATURAL COMPOUNDS IN CANCER TREATMENT

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Keywords:

Cancer,
Natural compounds,
Genetic, Epigenetic changes

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ABSTRACT: Today, cancer can be considered as a serious threat to human health because its treatment is difficult and expensive. Also, genetic modifications are considered as risk factors for many diseases including cancer. To discover a benefit and promising therapeutic is one of the main goals research on cancer. Environmental and nutritional factors can affect the organism through genetic and epigenetic changes. Natural compounds found in plants and can be a potential source for cancer treatment. It has recently been considered the role of some of these compounds in genetic and epigenetic changes. In this study, we mentioned some of these cases. This study is a beneficial review of the relationship between nutrition and cancer by searching for the related article.

INTRODUCTION: Nutrition is one of the most important factors affecting genetic and epigenetic. Many foods have properties of therapeutic and preventive against many diseases by interference in genetic and epigenetic processes. Cancer is one of the diseases that it has frequently been studied in this field. Many studies have been showed that nutritional factors found in fruits and vegetables lead to activation of tumor suppressor genes, apoptosis, and suppression of cancer genes through genetic and epigenetic processes [1, 2]. It has well been shown that food phytochemicals such as polyphenols, genistein, resveratrol, and curcumin could have had anti-cancer activity by effects of genetic and epigenetic [3, 4].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.IJP.4(8).257-61

The article can be accessed online on
www.ijpjournal.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.4(8).257-61

Dietary polyphenols found in fruits and vegetables are an essential part of the human diet [5]. Common polyphenols such as epigallocatechin gallate (EGCG), curcumin and resveratrol in green tea, turmeric and grape, respectively have a pivotal role in reducing and preventing cancer so that they inhibit DNA methyltransferase (DNMT) and lead to changes in the histones [6, 7]. The study aimed to review the effect of natural compounds on cancer by focusing on epigenetic processes.

Review Method: In this review study, we searched paper related to the role of natural compounds in the treatment of cancer with keywords such as natural compounds and cancer, natural compounds and epigenetic change during cancer in databases include the web of science, PubMed and Scopus. Then, the papers were fully read and summarized here.

The Effects of Natural Compounds in Cancer Treatment: There is resveratrol in food and normally in several plants, including peanut,

strawberry, blueberry, however it has majority been seen in grape peel [8]. The properties such as antioxidant, anti-inflammation and anti-cancer related to resveratrol occur through different biochemical and molecular pathways [9]. Also, the anti-proliferative property of resveratrol against cancers of breast, prostate, lung, and colon has been reported [10, 11].

Studies have been showed inhibitory effects of resveratrol on DNMT is lower than EGCG. However, resveratrol inhibits inactivation of BRCA1 as tumor suppressor genes [12]. Resveratrol activates the SIRT1 and P300 that known as a histone deacetylase inhibitor [13]. Histone deacetylases are responsible for removing acetyl groups from lysine in histone structure. To date, it has been identified at least 18 isozymes of histone deacetylase, which categorize in several class. In several studies, it has been reported the association between its class I with progressing of malignant tumors, but this association has been less in its class II [14]. Many studies have been examined the effects of resveratrol against aging. Based on study performed by Baur *et al.*, 2006 resveratrol could increase longevity and health in mice with a high-calorie diet [15]. Today than in the past, it has been confirmed the antioxidant activity of resveratrol. It inhibits oxidative damage against DNA in the presence of iron and copper [16].

The Brassicaceae family is rich in glucosinolate. Hydrolysis glucosinolate by myrosinase leads to the production of indole and isothiocyanate [17]. According to studies, isothiocyanate has pre-apoptotic and anti-proliferative properties and anti-carcinogenic effects [18]. Treatment with isothiocyanate leads to improvement of tumorigenesis in esophageal [19]. Allyl isothiocyanate found in broccoli can increase histone acetylation in mice's erythroleukemia cells. Phenylhexyl isothiocyanate as a synthetic isothiocyanate inhibits histone deacetylase, hypomethylation P16 and hyper-methylation histone H3 [20]. Also, phenylhexyl Isothiocyanate is affected in p21 activation, cell cycle arrest in prostate cancer and leukemia cells by inhibition of histone deacetylase activity required for chromatin remodeling [21]. Sulforaphane is another isothiocyanates, which is found in the Brassicaceae family such as broccoli. The studies have been showed that it has anticancer activity [22, 23]. Sulforaphane can induce apoptosis and influence cell cycle through inhibition of histone deacetylase; thus; it is involved in the regulation of cancer-related genes [24, 25]. Based on previous studies, treatment with sulforaphane inhibits histone deacetylase activity in prostate cancer. It also leads to inhibition of DNA methyltransferase in breast cancer and expression of the human telomerase gene in (Htert) in more than 90% of cancer [26, 27].

Isoflavones (genistein) are a group of flavonoids; in fact, they are the largest class of polyphenols. Polyphenols found in some plants such as soybean. Study on isoflavones has been showed that they have anti-cancer property. Among the isoflavones, most studies have been conducted on genistein, and it has been found that genistein as a phytoestrogen can be a promising compound to prevent cancer [28]. Several mechanisms have been attributed to the anti-cancer effects of genistein, including the ability to regulate genes transcription, DNA methylation and histone acetylation [29]. The studies on prostate cancer cells have been demonstrated that genistein results in the expression of tumor suppressor genes (p21 and p16) by changes in histone methylation [30]. Genistein inhibits DNA methyltransferase (DNMT1 3a, 3b) and increases the acetylation through an increment of histone acetyltransferase activity. Also, genistein and other isoflavones lead to regulation of miRNA expression in cancer cells [31, 32].

Curcumin is a polyphenol that turmeric is its source so that curcumin is responsible for the yellow color of turmeric. Curcumin has anti-inflammatory, antioxidant and anti-cancer properties and it is used as a therapeutic agent in Indian and Chinese medicine [33, 34]. Evidence suggests that curcumin as an affecting factor on DNA hypomethylation lead to facilitation of proto-oncogene expression [35, 36]. Curcumin has epigenomic effects in cancer cells because overall epigenetic methylation has been seen after treatment curcumin [37]. Also, it leads to the expression of GADD 153 and induction of apoptosis in lung cancer cells [38]. Curcumin inhibits histone acetyltransferase and histone deacetylase so that these events lead to changes in the histones.

According to performed studies, treatment with curcumin results in inhibition of histone acetyltransferase activity and ultimately the

reduction of acetylation in histones H3 and H4 in brain cells. Also, curcumin is main factor histone methylation in several promoters and inactivation of several genes. Recent studies have been demonstrated that inhibition of histone acetyltransferase has a possible role in cancer treatment. This view is a strong strategy for the treatment of cancer through cell cycle arresting and apoptosis induction [39, 40]. Several studies have been indicated that curcumin can inhibit the activity of p300/CBP in leukemia and uterus cancer [41]. There is also evidence that curcumin inhibits histone hypermethylation by histone deacetylase inhibitor in peripheral blood lymphocytes and cancer cells [42].

In previous studies, it has been reported that compounds in tea can prevent many diseases such as cancer. Indeed, tea contains polyphenolic compounds that have a protective effect against reactive oxygen species [3]. Epigallocatechin gallate (EGCG) comprises over 50% active ingredients of tea, and its anti-cancer activity has been widely studied [43,] and its preventive effect against cancer has been proven [44, 45]. Epigallocatechin gallate (EGCG) acts as anti-cancer compounds through several different mechanisms such as apoptosis induction, cell cycle arrest, reduction of oxidative stress, inhibition of proliferation and angiogenesis of cancer cells [46 - 49].

Based on previous studies that Epigallocatechin gallate (EGCG) reduces DNMT activity in esophageal cancer cells that leads to hyper-methylation of tumor suppressor genes and subsequently increase their activity [50]. EGCG results in a reduction of acetylation in p65 as a transcription factor by inhibition of histone acetyltransferase that this event leads to inhibition of inflammation due to reduction of NF-Ƙb and IL-6 levels [49]. Also, it increases the expression of tumor suppressor genes through the promotion of hypermethylation status in oral squamous cell carcinoma cells [51]. Moreover, Studies have been revealed that EGCG makes moderation of miRNA expression in liver cancer [52].

CONCLUSION: In this study, we reviewed the anticancer effects of natural compounds in the diet, which can be effective on important processes involved in the initiation and progression of cancer. Numerous studies have been showed that cancer alike other chronic diseases such as diabetes, cardiovascular disease are associated with metabolic stress and chronic inflammation. Also, the expression of genes involved in inflammation is controlled by epigenetic mechanisms. Natural compounds in the diet moderate inflammatory genes expression by an effect on epigenetic processes.

Based on empirical and laboratory evidence mentioned in this review, epigenetic changes are one of the main mechanisms related to natural compounds to control growth tumor and metastasis. Epigenetic changes lead to a lack of normal regulation of genes expression, oncogenes activation, and inhibition of tumor suppressor genes in early and advanced stages of carcinogenesis. Therefore, natural compounds are useful in order to prevention and treatment of cancer and can be effective in the development of new drugs against cancer. Results of performed studies in this field manifest a dire need to consume natural products to health promotion.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding this paper.

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How to cite this article:
Hassanpour SH and Roohipoor A: Review study on role of natural compounds in cancer treatment. Int J Pharmacognosy 2017; 4(8): 257-61. doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.4(8).257-61.