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ORIGINAL ARTICLE

Resveratrol in lung cancer- a systematic review

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Summary

Purpose: *Resveratrol, a phytochemical known for its anti-oxidative properties has been explored worldwide for anticancer potential. We performed this systematic review and meta-analysis in order to register the efficacy of resveratrol against lung carcinogenesis.*

Methods: *We searched PubMed for preclinical studies reporting efficacy of resveratrol alone or in combination with drugs like curcumin, cisplatin etc. against lung carcinogenesis.*

Results: *The primary outcome of eligible studies included change in overall tumor incidence as well as tumor size. In all of the above studies involving either animal models or in vitro cancer cell experiments a statistically significant reduction in tumor incidence emerged as compared with the control groups, yielding a relative risk reduction of 0.64 (p=0.002). This meta-analysis confirmed the potential of resveratrol against lung carcinogenesis.*

Conclusion: *It can be concluded that resveratrol holds a good potential for future use as a highly efficient therapeutic agent to deal with deadly lung carcinogenesis.*

Key words: *combination therapy, lung cancer, meta-analysis, resveratrol*

Introduction

Lung cancer is responsible for a tremendous number of deaths in both men and women [1,2]. These days, anticancer research is being focused on the utilization of novel combinations of variable approaches [3]. One of the upcoming strategies is combined chemoprevention. The idea is to sensitize cancer cells prior to the application of therapy in order to increase treatment efficacy with minimal side effects.

Resveratrol is an upcoming chemopreventive phytochemical being used in these novel combination strategies [4-7]. Phytochemicals are non-nutritional products of plants and are presently being studied around the world for their chemopreventive activities for controlling various diseases including cancer. The present systemic review aimed at evaluating the unique anticancer properties of resveratrol, especially against lung cancer, in various preclinical studies in the recent past. Resveratrol has shown several effective properties against carcinogenesis as reported in various earlier studies [8-11].

The purpose of this study was to search for important preclinical studies of the recent past in order to clarify the efficacy of resveratrol against lung carcinogenesis [12-16].

Methods

Literature search

We searched the literature for randomized controlled preclinical studies utilizing resveratrol against lung cancer or lung cancer cells. The most prominent electronic database searched for the purpose of the study was PubMed/Medline, followed by Embase, Cochrane Central Register of controlled Trials (issue 4, 2014) and CNKI. The choice of language was kept to English and Chinese only. The searched keywords were:

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resveratrol, combination therapy, lung cancer, management, preclinical studies. The studies with the following features were selected for the systematic review: A: the study should be a prospective randomized trial; B: the study should include the utilization of resveratrol against lung cancer.

Data extraction

The end points of interest in data extraction included overall efficacy against lung cancer in terms of prevention of carcinogenesis, decrease of carcinogenesis etc, in cell lines and preclinical models. Also, information of the first author's name, year of publication and the effect of resveratrol were registered.

Statistics

The random effect model was used in the analyses. Relative risk and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel and DerSimonian-Laird methods. The Cochran Q test was used to test heterogeneity. The publication bias was assessed by Begg's funnel plot and visual assessment of the funnel plot was calculated by RevMan 5.1 software. P values <0.05 were considered statistically significant.

Results

General characteristics of the studies

Five studies were finally included in this meta-analysis involving utilization of resveratrol against lung carcinogenesis. Detailed information of the included studies is shown in Table 1.

Therapeutic efficacy in lung cancer

Preliminary analysis showed some heterogeneity and so 5 studies involving cancer models as well as *in vitro* non-small cell lung carcinoma (NSCLC) cell lines were included in the analysis (Table 2). Overall, resveratrol treatment resulted in statistically significant reduction of carcinogenesis via prevention of oxidative stress as well as inflammation. When resveratrol groups were compared with the control groups a relative risk reduction ratio of 0.64 (range 0.45-0.81; p=0.002) was noticed.

There was no evidence of publication bias in the overall analysis. Figure 1 shows the risk bias graphs for visual assessment of the funnel plot using RevMan 5.1 software.

Discussion

Resveratrol has proved its efficacy in the prevention of carcinogenesis directly as well as indirectly in combination therapy. In both strategies, i.e. chemoprevention and chemotherapy, it resulted in significant reduction in tumor incidence and helped in enhancing the chemotherapeutic efficacy. A recent metaanalysis used in this review showed that resveratrol successfully enhanced the efficacy of cisplatin therapy by promoting cell death via apoptosis and mitochondrial dysfunction [14]. Furthermore, another group recently reported on a new resveratrol analogue that is able to inhibit gefitinib-resistant NSCLC by promoting increased intracellular calcium concentration [12]. In addition, Zhang et al. recently confirmed the ability of resveratrol to induce autophagy as well as apoptosis in lung cancer cells [15]. In an animal lung cancer model study, resveratrol in combination with curcumin has been reported to inhibit lung carcinogenesis by p53 post-translational modification [13]. Moreover, in human lung adenocarcinoma cells trans-resveratrol has been observed to induce apoptosis [16]. A recent report has suggested stimulation of suicide gene therapy with resveratrol treatment in lung cancer cells [17]. So, all these latest confirmations of anticancer activities of resveratrol favor its therapeutic use in the clinical setting.

We performed meta-analysis of some recent studies involving the use of resveratrol either alone or with a phytochemical, chemotherapy or

Table 1. General characteristics of the five studies

Study	*Publication year*	*Study methods*
Fan et al [12]	2015	*In vitro* cancer cells
Malhotra et al [13]	2014	Lung cancer model*
Mai et al [14]	2015	*In vitro* cancer cells
Zhang et al [15]	2015	*In vitro* cancer cells
Lucas and Kolodziei [16]	2015	Adenocarcinoma epithelial cells**

*in vivo , **in vitro

Table 2. Effect size (resveratrol efficacy) against lung carcinogenesis in all of the above studies

Study	*Weight %*	*Effect size (95% CI)*	*p value*
Fan et al [12]	31.5	0.70 (0.61,0.82)	0.002
Malhotra et al [13]	13.4	0.87 (075,0.98)	0.005
Mai et al [14]	21.5	0.49 (0.36,0.61)	0.003
Zhang et al [15]	23.9	0.64 (0.42,0.81)	0.002
Lucas and Kolodziei [16]	9.01	0.68 (0.45,0.81)	0.002

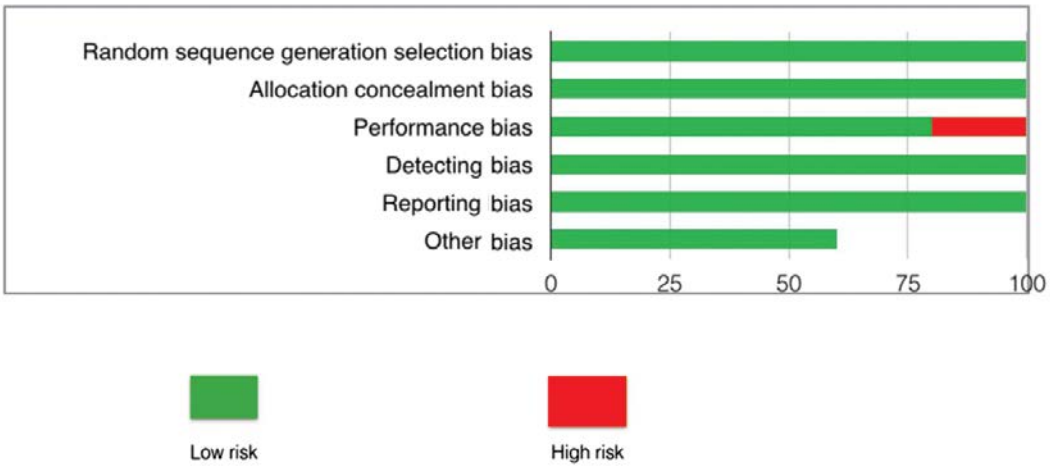

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

radiation therapy against lung carcinogenesis and the results confirmed its anticarcinogenic activity.

The prominent backbone of this anticancer potential of resveratrol should be attributed to its ability to inhibit the anti-inflammatory effects that accompany cancer [17,18]. Also, its capability to stimulate antioxidant enzymes has also contributed a lot in reversing the process of carcinogenesis by preventing oxidative stress during lung carcinogenesis [19]. Furthermore, resveratrol treatment resulted in stimulation of caspases, enhancement of tumor suppressor activities, induction of autophagy and maintenance of trace elements concentration [6,13,20,21]. So, the supplementary anticancer effects of resveratrol might make it a new therapeutic agent in the clinical setting in the near future. However, further investigations are still needed to make a concrete decision since studies available showing positive effects are mostly preclinical including animal models or *in vitro* cancer cell experimentations.

Therefore, from this meta-analysis it can be concluded that resveratrol is an upcoming alternative therapeutic agent against cancer and holds strong potential for its utilization in the clinical setting. However, more studies are required to draw sound conclusions.

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Conflict of interests

The authors declare no confict of interests.

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