Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 589 (2005) 81–102
Reviews in Mutation Research
www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

# Induction of apoptosis in tumor cells by naturally occurring sulfur-containing compounds

Xinjiang Wu, Fekadu Kassie, Volker Mersch-Sundermann*

*Faculty of Medicine, Institute of Indoor and Environmental Toxicology, Justus-Liebig-University of Giessen, University Hospital, Aulweg 123, D-35385 Giessen, Germany*

Received 27 July 2004; received in revised form 3 November 2004; accepted 3 November 2004
Available online 4 January 2005

**Abstract**

Chemoprevention is regarded as one of the most promising and realistic approaches in the prevention of human cancer. Among naturally occurring products, sulfur-containing compounds (OSCs), especially garlic compounds (GCs) and isothiocyanates (ITCs), represent two important and promising chemopreventive families because of their potent chemopreventive effects in various in vivo and in vitro models. In recent years, numerous investigations have shown that sulfur-containing compounds induce apoptosis in multiple cell lines and experimental animals. In the course of apoptosis induction by GCs and ITCs, multiple signal-transduction pathways and apoptosis intermediates are modulated. In particular, modulation of MAPKs and production of reactive oxygen species (ROS) seem to play pivotal roles in apoptosis induction by most GCs and ITCs. However, the role of P53 is still controversial. Based on present knowledge, GCs and ITCs may target not only the metabolism of carcinogens but also apoptosis signaling molecules. The effects of ITCs and GCs at multiple points of cancer development make these compounds highly promising candidates in cancer chemoprevention. However, the mechanisms of their anticancer effects are not fully understood, and further studies are required, especially to elucidate the role of cell-death receptors (the extrinsic pathway) and whether these agents induce apoptotic effects in non-tumor cells.


*Keywords:* Apoptosis; Sulfur containing compound; Garlic constituents; Isothiocyanates

*Abbreviations:* AITC, allyl-isothiocyanate; ARE, antioxidant response element; BITC, benzyl-isothiocyanate; DADS, diallyl disulfide; DAS, diallyl sulfide; DATS, diallyl trisulfide; HSPs, heat shock proteins; JNK, c-Jun N-terminal kinases; MAPKs, the mitogen-activated protein kinases; NAC, *N*-acetylcysteine; NAG-1, nonsteroidal anti-inflammatory drug (NSAID)-activated gene; NF-κB, nuclear factor kappa B; OSCs, organosulfur compounds; PARP, poly(ADP-ribose) polymerase; PBITC, phenylbutyl isothiocyanate; PEITC, phenylethyl isothiocyanate; PHITC, phenylhexyl isothiocyanate; PITC, phenyl isothiocyanate; PMITC, phenylmethyl isothiocyanate; PPITC, phenylpropyl isothiocyanate, 4-phenylbutyl isothiocyanate; ROS, reactive oxygen species; SAC, *S*-allylcysteine; SFN, sulforaphane; SMAC, *S*-allylmercaptocysteine

* Corresponding author. Tel.: +49 641 99 41400; fax: +49 641 99 41409.
*E-mail address:* volker.mersch-sundermann@uniklinikum-giessen.de (V. Mersch-Sundermann).

1383-5742/$ – see front matter 
doi:10.1016/j.mrrev.2004.11.001

**Contents**

1. Introduction . . . 82

2. Apoptosis induction by garlic constituents . . . 83
   2.1. Dially disulfide . . . 86
   2.2. Ajoene . . . 87

3. Apoptosis induction by isothiocyanates (ITCs) . . . 88
   3.1. Phenethyl isothiocyanate . . . 93
   3.2. Sulforaphane . . . 94

4. Conclusions and perspectives . . . 94
   4.1. Apoptosis induction by OSC in non-tumor cells . . . 94
   4.2. The role of death receptors pathway in OSC mediated apoptosis . . . 95
   4.3. Role of heat shock proteins in OSC mediated apoptosis . . . 96
   4.4. The role of survivin in OSC-mediated apoptosis . . . 96

References . . . 96

## 1. Introduction

In the last decades, mounting evidence from mechanistic studies of cancer helped to develop new promising chemopreventive agents. On the basis of the mechanism through which they exert anticancer effects, chemopreventive agents can be divided into two groups: antimutagenic and antiproliferative [1]. Antimutagens reduce formation of mutagens or carcinogens thereby preventing DNA damage. For instance, ROS scavenging and alteration in carcinogen metabolism (through suppression of phase I enzymes or enhancement of phase II detoxifying enzymes) represent antimutagenic effects. Alternatively, chemopreventive agents may exert antiproliferative effects via induction of cell cycle arrest or apoptosis, inhibition of angiogenesis, induction of terminal differentiation, and inhibition of oncogene activity or DNA synthesis [2]. Recent chemoprevention strategies are more concerned with identifying substances with antiproliferative or antiprogressive activities [3]. In particular, apoptosis, a physiological model of cell death, in which the cell itself executes the program for its own demise and subsequent removal, is an active field of research worldwide by scientists engaged in the search for cancer chemopreventive agents. Numerous studies demonstrated that evasion of apoptosis is one of the most important mechanisms of uncontrolled growth of tumor cells and resistance to the immune system. Hence, apoptosis of initiated and/or neoplastic cells represents a protective mechanism against neoplastic transformation and development of tumors through elimination of genetically damaged cells or cells that may have been inappropriately induced to divide by mitogenic and proliferative stimuli [4]. In the last decade, considerable attention has been focused on manipulation of apoptosis as a novel and promising strategy for cancer chemoprevention and therapy [5–9]. To achieve this goal, different naturally occurring compounds such as resveratrol, curcumin and genistein have been studied and were found to induce apoptosis in malignant cells [10–12]. A lot of such compounds exist in vegetables or fruits that are consumed by humans on a daily basis. Therefore, apoptosis induction by these agents in pre-cancerous and cancerous cells will undoubtedly contribute to chemoprevention. Clarification of the molecular mechanisms responsible for these effects may lead to the development of novel chemopreventive agents.

Among the many established naturally occurring dietary chemopreventive agents, the anticancer effects of sulfur-containing compounds (OSC) such as garlic constituents (GCs) and isothiocyanates (ITCs) have been widely reported. Besides their well-known effect in modulating phase I and II enzymes, GCs and ITCs