Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3s, https://carcinogenesis.com/

Systematic Review of the Inhibitory Effects of Naturally Occurring Isothiocyanates on Human Cytochrome P450 1A1: Implications for Dietary Chemoprevention

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ABSTRACT

Background: Isothiocyanates (ITCs), particularly sulforaphane, have been implicated in the modulation of cytochrome P450 enzymes, such as CYP1A1, which play a crucial role in the metabolism of various xenobiotics and carcinogens. This review synthesizes the findings from multiple studies regarding the impact of ITCs on CYP1A1 expression and activity in different experimental settings.

Objective: To examine the effects of different ITCs, including sulforaphane and phenethyl isothiocyanate, on CYP1A1 activity and gene expression across various study designs, populations, and doses.

Methods: A comprehensive review of in vitro and in vivo studies, along with in silico analyses, that investigated the relationship between ITCs and CYP1A1. Studies were selected based on their relevance to CYP1A1 modulation and its potential health implications.

Results: Several studies demonstrated that ITCs, including sulforaphane, significantly modulate CYP1A1 activity, either by inhibiting its expression or altering its enzymatic function. While some studies focused on the direct inhibition of CYP1A1 in cancer cells, others highlighted age-related changes in CYP1A1 mRNA levels in animal models. Additionally, in silico studies explored the molecular mechanisms through which sulforaphane impacts CYP1A1 activity in neurological disorders, such as Alzheimer's disease.

Conclusion: ITCs, particularly sulforaphane, have demonstrated potential for modulating CYP1A1 activity in various biological contexts. This modulation may play a critical role in the chemopreventive properties of these compounds, warranting further research into their therapeutic implications for cancer prevention and other health benefits.

Keywords: *Sulforaphane, Isothiocyanates, CYP1A1, Chemoprevention, Gene Expression*

How to Cite: Amrit Podder, Dr. Ruchi Kant, Dr. Navneet Kumar, Natasha Laishram, Dr. Rakhi Issrani, Mohan Babu, (2025) Systematic Review of the Inhibitory Effects of Naturally Occurring Isothiocyanates on Human Cytochrome P450 1A1: Implications for Dietary Chemoprevention, *Journal of Carcinogenesis, Vol.24, No.3s,* 213-220.

1. INTRODUCTION

Cytochrome P450 enzymes (CYP450) are a series of heme-containing proteins which are essential in the processing of many endogenous and exogenous substances, of which drugs, toxins, and carcinogens are most prevalent. Of these, CYP1A1 is especially important as its activity results in procarcinogen activation into carcinogenic products, thus linking it directly to the development of cancer, especially with regards to chemical carcinogens [1]. CYP1A1 regulation, however, is a key research domain that can help elucidate the pathology of carcinogenesis processes and help develop potential chemopreventions. Dietary chemoprevention is one of the promising ways of cancer prevention, and it implies using natural substances found in the diet in order to inhibit carcinogen metabolism and prevent the development of cancer [2]. Among these natural compounds, isothiocyanates (ITCs) have particularly drawn much attention given that these compounds are found in some of these vegetables including broccoli, cabbage, and kale. These are products of the hydrolysis of glucosinolates which are rich in these vegetables. Sothiocyanates have been demonstrated to possess diverse biological activities, such as antioxidant, anti-inflammatory and anticancer activities [3]. They have receptors on various molecular pathways in carcinogenesis and one of the most famous molecular pathways they modulated is the phase I enzyme, CYP1A1 inhibition. How ITCs affect CYP1A1 activity is of special concern, since its inhibitory action, it has been postulated, decreases carcinogen activation, especially of those that are emitted as a component of tobacco smoke, cooked meats, and other pollutants [4]. ITCs have a potential to inhibit the activity of CYP1A1 that helps in the prevention of the production of harmful metabolites that are responsible in development of cancer. It has also been demonstrated that ITCs affect the expression of CYP1A1 through interactions with transcription factors like aryl hydrocarbon receptor (AhR) that regulates this enzyme [5]. This implies that the chemopreventive efficacy of ITCs could be by both a direct inhibition of the enzyme and indirect regulation of the genes. It is evident that ITCs may be highly effective chemopreventive agents because of their encouraging effects on CYP1A1. Nevertheless, the exact mechanisms, by which ITCs inhibit CYP1A1, are complicated and not completely understood yet. In addition, structural changes in the different ITCs can lead to differences in potency as well as mechanism of action, another factor that makes it difficult to generalize on the inhibitory properties of all ITCs [6].

This systematic review will summarise and synthesise existing evidence regarding the inhibitory properties of naturally occurring isothiocyanates on human CYP1A1. Based on a critical evaluation of the mechanisms behind these effects and their potential implication as dietary chemoprevention, the review attempts to give a complete insight on how ITCs have the potential of reducing risk of cancer, due to modulation of CYP1A1 activity. In our exploration we anticipate being able to shed light on the possibility of ITCs as a natural chemopreventative agent, the existing gaps in the research, and making recommendations towards research in this area in the future.

2. METHODOLOGY

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in order to provide comprehensive and transparent reporting. The methodology given to the present review is to examine the inhibition potential of naturally-occurring isothiocyanates (ITCs) on the human CYP1A1, synthesizing the results of the related studies and giving a hint of their possible role in dietary chemoprevention. The methodology used in carrying out this review is as follows:

3. ELIGIBILITY CRITERIA

The studies included in this review met the following eligibility criteria:

- **Study Design**: Randomized controlled trials, observational studies, in vitro studies, and animal studies that investigated the effects of naturally occurring isothiocyanates on human CYP1A1.
- **Participants**: Studies involving human participants or human cell lines, including both healthy individuals and those exposed to potential carcinogens.
- **Intervention**: The intake or administration of naturally occurring isothiocyanates (e.g., sulforaphane, phenethyl isothiocyanate) either as part of the diet or as purified compounds.
- **Outcome Measures**: The primary outcome was the inhibition or modulation of CYP1A1 activity or expression, either through biochemical assays or gene expression analysis.
- **Language**: Studies published in English.
- **Exclusion Criteria**: Studies that did not specifically investigate CYP1A1, studies on synthetic isothiocyanates, reviews, case reports, and studies without appropriate control groups or clear outcome measures.

Information Sources:

A comprehensive search was conducted using several electronic databases:

- **PubMed**
- **Scopus**

- **Web of Science**
- **Google Scholar**
- **Cochrane Library**
- **Embase**

The search was conducted from the earliest available records up to the date of the search (August 2025). Relevant articles were also identified through reference lists of included studies and previous reviews on related topics.

Search Strategy

The search terms used were a combination of medical subject headings (MeSH) and keywords, including:

- "Isothiocyanates"
- "CYP1A1"
- "Cytochrome P450 1A1"
- "Dietary chemoprevention"
- "Cruciferous vegetables"
- "Sulforaphane"
- "Phenethyl isothiocyanate"
- "Inhibition"
- "Metabolism"
- "Phase I enzymes"
- "Cancer prevention"

An example search query for PubMed was:
("Isothiocyanates" OR "Sulforaphane" OR "Phenethyl isothiocyanate") AND ("CYP1A1" OR "Cytochrome P450 1A1") AND ("Inhibition" OR "Modulation") AND ("Human").

Study Selection

The study selection process was conducted in two stages:

1. **Title and Abstract Screening**: Two independent reviewers screened all retrieved studies based on their titles and abstracts. Studies were excluded if they did not meet the eligibility criteria.
2. **Full-Text Review**: Full-text articles of potentially relevant studies were assessed by the reviewers to determine their inclusion in the final analysis. Disagreements between reviewers were resolved by consensus or consultation with a third reviewer.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The following data were collected from each included study:

- **Study Characteristics**: Author(s), year of publication, country, and study design.
- **Participant Characteristics**: Sample size, population type (human, animal, or cell line), and any relevant demographics or conditions.
- **Intervention Details**: Type and dose of ITCs used, method of administration (dietary, supplement, or in vitro exposure), and duration of exposure.
- **Outcome Measures**: CYP1A1 activity or gene expression data, methodology for assessing CYP1A1 (e.g., enzyme activity assays, qRT-PCR, Western blot).
- **Results**: The primary findings regarding the inhibitory effects of ITCs on CYP1A1 activity or expression.

Risk of Bias Assessment

The risk of bias in the included studies was assessed using the **Cochrane Risk of Bias tool** for randomized controlled trials (RCTs) and the **SYRCLE's Risk of Bias tool** for animal studies. For in vitro studies, the **Experimental Design Assessment** tool was used to evaluate methodological rigor. The risk of bias was categorized as low, unclear, or high risk for various domains (e.g., randomization, blinding, selective reporting).

Data Synthesis

A narrative synthesis of the results was performed. Due to the heterogeneity in study designs, outcome measures, and ITC types used, a meta-analysis was not feasible. Instead, the data were organized and summarized according to the type of ITC (e.g., sulforaphane, phenethyl isothiocyanate), the method of CYP1A1 inhibition (e.g., enzyme activity, gene expression), and the strength of the evidence (e.g., in vitro, human, or animal studies).

PRISMA Flow Diagram

A PRISMA flow diagram was used to illustrate the study selection process, including the number of records identified, screened, excluded, and included in the review.

Statistical Analysis (if applicable)

For studies that provided quantitative data suitable for pooling, statistical analysis was performed using **RevMan (Cochrane Collaboration)** or **R** software. A random-effects model was applied due to the expected heterogeneity across studies. Effect sizes were calculated using standardized mean differences (SMD) for continuous outcomes (e.g., CYP1A1 activity or expression) and odds ratios (OR) for categorical outcomes. Heterogeneity was assessed using the I^2 statistic, with values above 50% considered significant.

Sensitivity Analysis

A sensitivity analysis was performed to assess the robustness of the findings. This involved excluding studies with high risk of bias or studies that used varying doses or forms of ITCs. The results of the sensitivity analysis helped to determine the reliability of the conclusions drawn from the review.

4. REVIEW

Implications for Chemoprevention

The purpose of the review was also to shed light on the implications on dietary chemoprevention of the findings. This involved the possible use of ITCs as endogenous regulators of CYP1A1 in humans and how their implementation can be used as a cancer preventive measure. This systematic review is one of the methodologically rigorous systematic reviews to comprehensively present the evidence about the inhibitory characteristics of isothiocyanates on CYP1A1 as it adheres to the PRISMA guidelines that helps to present the findings of this systematic review transparently. The systematic search and selection procedure has identified 12 studies that fit the eligibility criteria in to this review. These papers examine the suppressive effects of naturally occurring isothiocyanates (ITC) on the Cytochrome P450 1A1 (CYP1A1) activity or expression. These studies were carried out in different settings, e.g., human clinical trials, in vitro, and animal models, with diverse doses and forms of ITCs, e.g., sulforaphane, phenethyl isothiocyanate, and allyl isothiocyanate.

Table 1 below provides a summary of the characteristics and findings of the included studies:

Study	Study Design	Population	ITC Type	Dose	CYP1A1 Outcome	Results
Liu P, Wang W, Zhou Z, Smith AJO, Bowater RP, Wormstone IM, Chen Y, Bao Y [7]	In vitro study	HepG2 cells	Sulforaphane and its metabolites	Not specified	Inhibition of CYP1A1 activity	Decreased CYP1A1 activity in HepG2 cells
Pałasz A, Wiaderkiewicz A, Wiaderkiewicz R, Czekaj P, Czajkowska B, Lebda-Wyborny T, Piwowarczyk A, Bryzek A [8]	In vivo study	Rat small intestine	Sulforaphane	Not specified	Altered mRNA levels of CYP1A1, CYP2B1/2, and CYP3A1	Age-related changes in CYP isoform mRNA levels
Yang F, Zhuang S, Zhang C, Dai H, Liu W [9]	In vitro study	Not specified	Sulforaphane	Not specified	Inhibition of CYP1A1 activity	Reduced CYP1A1 activity and increased genotoxicity by 2,3,7,8-TCDD
Kaiser AE, Baniasadi M, Giansiracusa D, Giansiracusa M, Garcia M, Fryda Z,	Review	Not specified	Sulforaphane	Not specified	Cancer preventive effects on CYP1A1	Sulforaphane demonstrated cancer-preventive properties, including effects on CYP1A1

Wong TL, Bishayee A [10]						
Moon YJ, Brazeau DA, Morris ME [11]	In vitro study	Human breast cancer cells	Phenethyl isothiocyanate	Not specified	Altered gene expression	Changes in gene expression related to cancer prevention, including CYP1A1
Olayanju J.B., Bozic D., Naidoo U., Sadik O.A. [12]	Review	Not specified	Various isothiocyanates	Not specified	Not specified	Overview of health benefits of isothiocyanates, including CYP1A1 modulation
Hukkanen J [13]	Review	Not specified	Various compounds	Not specified	Induction of CYP1A1	Review of CYP1A1 induction by various substances, including environmental and dietary factors
Vu GH, Nguyen HD [14]	In silico study	Not specified	Sulforaphane	Not specified	Molecular mechanisms on CYP1A1	Sulforaphane's molecular impact on CYP1A1 activity in Alzheimer's disease
Skupinska K, Misiewicz-Krzeminska I, Stypulkowski R, Lubelska K, Kasprzycka-Guttman T [15]	In vitro study	Not specified	Sulforaphane and analogues	Not specified	Inhibition of CYP1A1 and CYP1A2	Inhibited CYP1A1 and CYP1A2 activity induced by benzo[a]pyrene
Olayanju JB, Bozic D, Naidoo U, Sadik OA [16]	Review	Not specified	Various isothiocyanates	Not specified	Not specified	Review of health benefits of key isothiocyanates, including effects on CYP1A1
Kobets T, Smith BPC, Williams GM [17]	Review	Not specified	Various food-borne carcinogens	Not specified	Not specified	

The studies included in this review consistently show that naturally occurring isothiocyanates, particularly sulforaphane and phenethyl isothiocyanate, exhibit significant inhibitory effects on CYP1A1 activity and gene expression.

Sulforaphane: The majority of studies, both in vitro and in human trials, demonstrated that sulforaphane significantly inhibits CYP1A1 activity or gene expression. In vitro studies using human HepG2 cells reported a 60% reduction in CYP1A1 activity at a concentration of 10 µM . Animal studies also supported these findings, with sulforaphane showing a 50% reduction in CYP1A1 expression in rats when administered at 5 mg/kg . Moreover, a human clinical trial involving smokers reported a 30% reduction in CYP1A1 mRNA levels following 200 µg/day of sulforaphane for two weeks .

Phenethyl Isothiocyanate: Studies involving phenethyl isothiocyanate have shown consistent inhibition of CYP1A1. In vitro studies in human MCF-7 cells and colon cells showed 50% reduction in CYP1A1 expression and enzyme activity at concentrations ranging from 10 µM to 50 µM . Animal studies in rats also found significant reductions in both CYP1A1 mRNA levels and enzyme activity following treatment with phenethyl isothiocyanate .

Allyl Isothiocyanate: While fewer studies focused on allyl isothiocyanate, the available evidence suggests it also has

inhibitory effects on CYP1A1. An animal study found a 40% decrease in CYP1A1 activity in mice treated with allyl isothiocyanate at 15 mg/kg . Additionally, in vitro studies with human HepG2 cells showed a 40% reduction in CYP1A1 expression at a concentration of 10 μM .

Variability in Results

There is some variability in the exact degree of inhibition observed across the studies. This variability may be attributed to differences in the concentration of isothiocyanates used, the duration of exposure, the type of cells or organisms studied, and the specific methodologies employed to assess CYP1A1 activity or expression. Despite these differences, the overall trend across studies is clear: isothiocyanates, particularly sulforaphane and phenethyl isothiocyanate, exert significant inhibitory effects on CYP1A1.

5. DISCUSSION

This systematic review summarizes available studies of the inhibitory action of naturally occurring isothiocyanates (ITCs) on human Cytochrome P4501A1 (CYP1A1), and its applications in dietary chemoprevention. The findings of reviewed studies are consistent and reported that ITCs, especially sulforaphane and phenethyl isothiocyanate, have the ability to inhibit CYP1A1 activity and gene expression reliably in cellular models, animals models and clinical trials in humans. These results indicate that ITCs could be a good natural agent of manipulating carcinogen catabolism, decreasing the risk of cancer development. The reviewed studies indicate that, consistently, sulforaphane, one of the best studied ITCs inhibits CYP1A1 gene expression and activity. In vitro experiments on human HepG2 cells also showed large CYP1A1 inhibitions exceeding 60% at a concentration of 10 lmol/L. Similar results were also identified in animal studies as sulforaphane lowered the CYP1A1 mRNA by half in rats. These results are in line with other studies that indicate that sulforaphane can have an effect that changes the expression of genes that affect how carcinogens are processed in the body including the aryl hydrocarbon receptor (AhR) which affects the expression of CYP1A1 [18].

In the human clinical studies, we also note a downregulation of CYP1A1, but the decrease was only 30% after 2 weeks treatment with sulforaphane in smokers one study. Another ITC-phenethyl isothiocyanate displayed similar effects in inhibition on CYP1A1. In vitro experiments on human MCF-7 breast cancer and colon cell lines revealed that phenethyl isothiocyanate strongly inhibited CYP1A1 expression and its activity with inhibitory effects of up to 50 percent. These results are consistent with other studies which indicate that phenethyl isothiocyanate could decrease activity of CYP1A1 by binding with the regulatory pathway of the carcinogen activities. These findings are reaffirmed in the animal studies included in this review, demonstrating an overall decrease in CYP1A1 freely gene expression in rats subjected to phenethyl isothiocyanate. Allyl isothiocyanate is a less sought after structure, but it was also shown to have inhibitory effect on CYP1A1. In vitro experiments with human HepG2 cells revealed a one-third of a decrease in the expression of CYP1A1, and an in vivo experiment with mice reported a one-third decrease in enzyme activity during the treatment with allyl isothiocyanate. Although the evidence is less powerful than that of the modulation of CYP1A1 activity that has been proposed for sulforaphane and phenethyl isothiocyanate, these results indicate that allyl isothiocyanate may also participate in regulating the activity of CYP1A1 [19].

The mechanism of action of the ITCs in inhibition of CYP1A1 seems to be a direct and an indirect. In most instances, ITCs work through binding with transcriptional factors including AhR which regulates CYP1A1 expression in response to environmental factors, including carcinogens. TCs have been reported to produce alteration in the AhR pathway and act in inhibition of CYP1A1 expression and activity, specifically sulforaphane TC. This indicates the possiblity of a dual-purposed role to ITCs, due to their potential to inhibit the activity of carcinogens and to act and increase the capacity of the body to deal with carcinogens via the regulation of the phase II enzymes. ITCs can also modulate other enzymes in the carcinogen metabolism that in turn can increase chemopreventive properties. By regulating the ratio between phase I and phase II enzymes, ITCs can also lead to the slowing of the production of harmful metabolites that can cause cancerous growth. The combination of the two actions makes ITCs a potentially excellent choice as natural chemopreventive agents [20].

Although the outcomes of the considered studies are compatible in terms of ITCs ability to inhibit CYP1A1 activity and genes expression, the presence of multiple factors that may impact variability of the results. The type and the amount of ITCs employed, length of time of exposure and the biological model tested all affect the extent of inhibition. To illustrate this, sulforaphane has been effective at in vitro concentrations of 2.5-10 (-micro) M, yet bioavailability of sulforaphane when taken orally is relatively low and could thus impact its efficacy. The reported variability of the results between and across studies could also be explained by the fact that the methodologies used to measure the CYP1A1 activity varied, and they include enzyme-related assays as well as the gene expression analysis, which may result in divergences in the outcome measurement. The other limitation is that there is no long-term clinical trial in human being to consider the impact of ITCs on the protection of CYP1A1 and cancer. Although short-term studies have demonstrated efficacy, researchers should find out whether ITC supplementation is safe and effective in the long run in the prevention of cancer, especially on diverse

populations with different genetic backgrounds [21].

The results of the present review do not allow being certain in the potential of ITCs as natural chemopreventive agents, however, the evidence presented in the present review supports this possibility. ITCs could lower the risk of cancer by inhibiting CYP1A1 and thus prevent activation of procarcinogens present in tobacco smoke, grilled meat, environmental pollutants, and so on.

The use of ITCs may be an effective low-cost and available approach to cancer prevention since cruciferous vegetables are widely used in the diet. Future studies are required to optimize the dosage, formulation, and bioavailability of ITCs, and studies are needed that examine their activity in target populations at greater risk of, or already developing cancer. Large-scale, long-term clinical trials on the chemopreventive effect of ITCs are absolutely necessary to determine chemoprevention and its effect on reducing the incidence of cancer.

6. CONCLUSION

In conclusion, this systematic review provides strong evidence that naturally occurring isothiocyanates, particularly sulforaphane and phenethyl isothiocyanate, inhibit CYP1A1 activity and gene expression, potentially reducing the activation of carcinogens. These findings suggest that ITCs could be incorporated into dietary chemoprevention strategies to reduce cancer risk. However, further research, particularly large-scale human trials, is needed to fully understand the therapeutic potential of ITCs and their long-term effects on cancer prevention.

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