Archives of Life Science and Nutritional Research
Review Article

# Effects of 3,3-Diindolylmethane Supplementation in cancer therapy: A narrative review

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## Abstract

3,3-Diindolylmethane (DIM) is a natural compound that is abundant in cruciferous vegetables such as broccoli and cabbage. DIM has been used in numerous animal models in cancer prevention, as well as in human clinical trials. The objective of this review is to verify the influence of DIM in the treatment of different types of cells and tumors of various types of cancer. The results show the positive effect that DIM intake has on different types of cancer such as: cell apoptosis, inhibition of tumor growth and improvements with combined chemotherapy treatment. In conclusion, commenting that the intake of DIM has beneficial effects in different types of cancer such as colorectal, gastrointestinal, breast, prostate and ovarian.

## Keywords: diindolilmethane, cancer, prostate, colon, ovarian and breast.

## Introduction

3,3-Diindolylmethane (DIM) (Figure 1) is a natural compound produced from the acid-catalyzed self-condensation of indole-3-carbinol, which is abundant in cruciferous vegetables such as broccoli and cabbage [1].

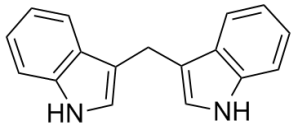


**Figure 1.** Structure of the diindolylmethane.

The biological activities and properties of DIM (Figure 2) have been the subject of high research interest. In addition to its outstanding chemotherapeutic activity, DIM has multiple properties: antiviral, antifungal, anti-leishmaniasis, anti-inflammatory, improves arthritis and promotes osteoclastogenesis [2].

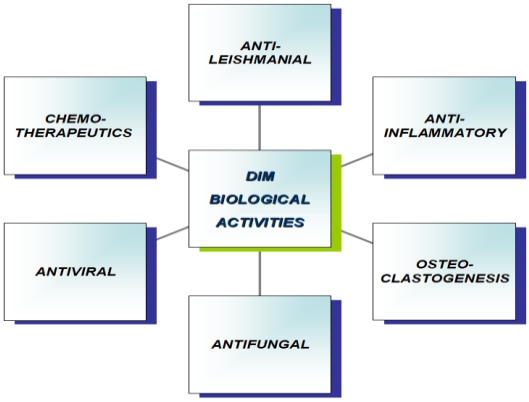


**Figure 2.** Biological activities of the diindolylmethane.

Cancer chemoprevention is an important cancer preventive strategy that uses natural dietary phytochemicals or therapeutic drugs with relatively low toxicity to inhibit malignant transformation of cells. Therefore, chemoprevention may involve preventing carcinogens from reaching target sites, undergoing metabolic activation, or subsequently interacting with crucial cellular macromolecules such as DNA, RNA, and proteins at the stage of cancer initiation. Interestingly, prevention and/or protection against chemical carcinogens by phytochemicals present in cruciferous vegetables containing glucosinolates is of great interest because they may provide a safe and cost-effective strategy to combat cancer. In this context, numerous epidemiological and pharmacological studies have revealed that the consumption of cruciferous vegetables has substantial potential for the chemoprevention of human cancer [3].

DIM has been used in numerous animal models of cancer prevention, as well as in human clinical trials, focusing mainly on breast and prostate cancer. Among the many pathways affected by DIM are those mediated by the aryl hydrocarbon receptor (AHR) and the estrogen receptor (ER) [4].

The objective of this review article is to carry out a broad and exhaustive analysis of the available scientific evidence on the role of DIM in the treatment of different types of cells and tumors of various types of cancer such as: colorectal, gastrointestinal, breast, prostate and ovary.

## Material and Methods

A descriptive review study has been carried out with the objective of answering the following research question: What effects does the intake of DIM have on the prevention and regression of different types of cancer?

For this, a search was done in Pubmed in April 2024. In order to find the largest number of articles possible, the following keywords were used: diindolilmethane, cancer, prostate, colon, ovarian and breast.

For the selection of articles, inclusion criteria were used such as: articles published in any country, articles published in English, articles where DIM is ingested in living beings with cancer and articles where the research is carried out in vivo and in vitro; The exclusion criteria were established: articles that do not clearly show the intake of DIM, articles that do not refer to cancer therapy.

# Results

## DIM Intake and Colorrectal Cancer

In a study led by Zhang et al. DIM treatment was shown to inhibit the malignant progression of colorectal cancer (CRC). DIM increases the cytotoxicity of 5-Fluoracil (5-FU) in CRC by regulating the expression of genes related to pyrimidine metabolism. DIM synergizes with 5-FU to enhance its inhibitory effects on CRC both in vivo and in vitro. Researchers suggest that DIM improves the therapeutic results of 5-FU-based chemotherapy in CRC with the combination 5FU + DIM being a new strategy for the clinical therapy of CRC [5].

The authors Bhatnagar et al. discovered that DIM is very effective in inhibiting survivin synthesis and is able to significantly enhance butyrate-induced apoptosis of colon cancer (CC) cells. DIM can be highly effective in preventing CC [6].

On the other hand, the authors Lee et al. concluded that DIM acted by inhibiting CC cell proliferation and inducing CC cell apoptosis [7].

Lerner et al. conducted research on colon cancer therapy using DIM, this study concluded that DIM induced apoptosis of human colon cancer cells and tumors [8].

In a recent study conducted by Clark et al. The possible synergistic effects of capsaicin in combination with DIM were evaluated. In this study, a synergistic induction of apoptosis and inhibition of cell proliferation in human CRC cells was observed through the combined administration of capsaicin and DIM [9].

## DIM and Gastrointestinal Cancer

The authors Ye et al. found that DIM produced growth inhibition of gastric cancer (GC) cells both in vitro and in vivo [10].

These results were confirmed by another study by Ye et al. where it was shown that DIM had an inducing effect on cell apoptosis and autophagy [11].

In the review study conducted by Kim et al. demonstrated that DIM acted on different cellular and molecular processes in gastrointestinal cancer cells such as: apoptosis, autophagy, cell cycle regulation, metastasis, angiogenesis, endoplasmic reticulum stress combined with other therapeutic treatments for gastrointestinal cancer (GIC) [12].

A study by Ye et al. showed how DIM intervenes in the modulation of TNF Receptor Associated Factor 2, providing a new therapeutic target for human GC [13].

Li et al. in their study provided strong evidence that DIM induces the death of human gastric cancer cells [14].

However, Zhu et al. concluded that low doses of DIM can promote the growth and progression of GC, so DIM at low doses can produce an adverse effect in cancer therapy, only high doses have shown favorable effects [15].

## DIM and Breast Cancer

Jin et al. stated in their study that DIM administration produced an inhibition of breast cancer (BC) cell proliferation, so DIM can arrest the cell cycle progression of human BC cells [16].

Rahman et al. found in their study that DIM inhibited cell growth and induced apoptosis of human BC cells MDA-MB-231 by negatively regulating the expression of survivin [17].

In the study by Zhu et al. demonstrated that the combination of AZD5363 with DIM could be developed as a potential therapy for BC [18].

According to Hong et al. DIM inhibited DNA synthesis and cell proliferation of 2 human BC cell lines: MCF-7 and MDA-MB-231 [19].

Penta et al. suggest in their study that DIM can be used as a dietary bioactive phytochemical against human BC [20].

The authors Saati et al. show in their study how DIM inhibits the proliferation of 3 human BC cell lines: MCF-7, MDA-MB-231 and SKBr-3 [21].

Scientific evidence of the protective role of DIM against BC continues to grow. However, researchers Thomson et al. suggest that information on specific DIM dosing is currently lacking [22].

## DIM Intake and Prostate Cancer

The study conducted by Nachshon-Kedmi et al. which aimed to examine the apoptotic pathways that may be involved in the effect of DIM on the prostate cancer (PC) cell line, showed that DIM induces apoptosis in human PC3 cells [23].

The objective of the study carried out by Fares et al. was to examine the effectiveness of DIM in preventing the development of PC tumors in an animal model. The results indicated that DIM significantly reduced tumor development in treated animals compared to controls [24].

The objective of the study carried out by Nachshon-Kedmi et al. was to examine the possible therapeutic effects of DIM in an in vivo mouse model. The results showed that DIM had a significant inhibitory effect on tumor growth [25].

## DIM and Ovarian Cancer

The authors Kandala et al. concluded in their study that DIM induces apoptosis in ovarian cancer (OC) cells by inhibiting STAT3 oncoprotein signaling [26].

Furthermore, these researchers in another study showed that DIM induces apoptosis in OC cells and suppresses the growth of ovarian tumors in vivo by inhibiting the epidermal growth factor receptor pathway [27].

## Conclusions and Future Directions

The conclusions of this review, it is highlighted that the intake of DIM has beneficial effects in differentes types of cancer, specifically:

- DIM intake induces apoptosis and inhibits cell proliferation in human CRC and CC cells.
- DIM is an inducer of apoptosis and inhibits the growth of GC cells.
- DIM inhibits cell growth and induces apoptosis of 3 human CB cell lines: MCF-7, MDA-MB-231 and SKBr-3.
- DIM has a significant inhibitory effect on tumor growth and induces apoptosis of PC cells.
- DIM induces apoptosis of OC cells and suppresses the growth of ovarian tumors.

Both DIM and other phytochemicals show great promise in the prevention and combined treatment of different types of cancer. Therefore, it is essential that there is greater scientific evidence on the effects of phytochemicals such as DIM on different types of cancer.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The author have no conflict of interest to declare.

# References

1. Choi KM, Yoo HS. Amelioration of Hyperglycemia-Induced Nephropathy by 3,3'-Diindolylmethane in Diabetic Mice. *Molecules*. 2019; 24(24):4474. doi:10.3390/molecules24244474

2. Golberg K, Markus V, Kagan BE et al. Anti-Virulence Activity of 3,3'-Diindolylmethane (DIM): A Bioactive Cruciferous Phytochemical with Accelerated Wound Healing Benefits. *Pharmaceutics*. 2022; 14(5):967. doi:10.3390/pharmaceutics14050967

3. Fuentes F, Paredes-Gonzalez X, Kong AN. Dietary Glucosinolates Sulforaphane, Phenethyl Isothiocyanate, Indole-3-Carbinol/3,3'-Diindolylmethane: Anti-Oxidative Stress/Inflammation, Nrf2, Epigenetics/Epigenomics and *In Vivo* Cancer Chemopreventive Efficacy. *Curr Pharmacol Rep*. 2015; 1(3):179-196. doi:10.1007/s40495-015-0017-y

4. Vermillion Maier ML, Siddens LK, Uesugi SL et al. 3,3'-Diindolylmethane Exhibits Significant Metabolism after Oral Dosing in Humans. *Drug Metab Dispos*. 2021; 49(8):694-705. doi:10.1124/dmd.120.000346

5. Zhang J, Zou S, Zhang Y, et al. 3,3'-Diindolylmethane Enhances Fluorouracil Sensitivity via Inhibition of Pyrimidine Metabolism in Colorectal Cancer. *Metabolites*. 2022; 12(5):410. doi:10.3390/metabo12050410

6. Bhatnagar N, Li X, Chen Y, Zhou X, Garrett SH, Guo B. 3,3'-diindolylmethane enhances the efficacy of butyrate in colon cancer prevention through down-regulation of survivin. *Cancer Prev Res*. 2009; 2(6):581-589. doi:10.1158/1940-6207.CAPR-08-0142

7. Lee SH, Min KW, Zhang X, Baek SJ. 3,3'-diindolylmethane induces activating transcription factor 3 (ATF3) via ATF4 in human colorectal cancer cells. *J Nutr Biochem*. 2013; 24(4):664-671. doi:10.1016/j.jnutbio.2012.03.016

8. Lerner A, Grafi-Cohen M, Napso T, Azzam N, Fares F. The indolic diet-derivative, 3,3'-diindolylmethane, induced apoptosis in human colon cancer cells through upregulation of NDRG1. *J Biomed Biotechnol*. 2012; 2012:256178. doi:10.1155/2012/256178

9. Clark R, Lee J, Lee SH. Synergistic anticancer activity of capsaicin and 3,3'-diindolylmethane in human colorectal cancer. *J Agric Food Chem*. 2015; 63(17):4297-4304. doi:10.1021/jf506098s

10. Ye Y, Fang Y, Xu W, Wang Q, Zhou J, Lu R. 3,3'-Diindolylmethane induces anti-human gastric cancer cells by the miR-30e-ATG5 modulating autophagy. *Biochem Pharmacol*. 2016; 115:77-84. doi:10.1016/j.bcp.2016.06.018

11. Ye Y, Li X, Wang Z, et al. 3,3'-Diindolylmethane induces gastric cancer cells death via STIM1 mediated store-operated calcium entry. *Int J Biol Sci*. 2021; 17(5):1217-1233. doi:10.7150/ijbs.56833

12. Kim SM. Cellular and Molecular Mechanisms of 3,3'-Diindolylmethane in Gastrointestinal Cancer. *Int J Mol Sci*. 2016; 17(7):1155. doi:10.3390/ijms17071155

13. Ye Y, Ye F, Li X, et al. 3,3'-diindolylmethane exerts antiproliferation and apoptosis induction by TRAF2-p38 axis in gastric cancer. *Anticancer Drugs*. 2021; 32(2):189-202. doi:10.1097/CAD.0000000000000997

14. Li XJ, Park ES, Park MH, Kim SM. 3,3'-Diindolylmethane suppresses the growth of gastric cancer cells via activation of the Hippo signaling pathway. *Oncol Rep*. 2013; 30(5):2419-2426. doi:10.3892/or.2013.2717

15. Zhu Y, Zhang B, Gong A, et al. Anti-cancer drug 3,3'-diindolylmethane activates Wnt4 signaling to enhance gastric cancer cell stemness and tumorigenesis. *Oncotarget*. 2016; 7(13):16311-16324. doi:10.18632/oncotarget.7684

16. Jin Y. 3,3'-Diindolylmethane inhibits breast cancer cell growth via miR-21-mediated Cdc25A degradation. *Mol Cell Biochem*. 2011; 358(1-2):345-354. doi:10.1007/s11010-011-0985-0

17. Rahman KW, Li Y, Wang Z, Sarkar SH, Sarkar FH. Gene expression profiling revealed survivin as a target of 3,3'-diindolylmethane-induced cell growth inhibition and apoptosis in breast cancer cells. *Cancer Res*. 2006;66(9):4952-4960. doi:10.1158/0008-5472.CAN-05-3918

18. Zhu K, Liu X, Liu C, et al. AKT inhibitor AZD5363 suppresses stemness and promotes anti-cancer activity of 3,3'-diindolylmethane in human breast cancer cells. *Toxicol Appl Pharmacol*. 2021; 429:115700. doi:10.1016/j.taap.2021.115700

19. Hong C, Firestone GL, Bjeldanes LF. Bcl-2 family-mediated apoptotic effects of 3,3'-diindolylmethane (DIM) in human breast cancer cells. *Biochem Pharmacol*. 2002; 63(6):1085-1097. doi:10.1016/s0006-2952(02)00856-0

20. Penta D, Mondal P, Natesh J, Meeran SM. Dietary bioactive diindolylmethane enhances the therapeutic efficacy of centchroman in breast cancer cells by regulating ABCB1/P-gp efflux transporter. *J Nutr Biochem*. 2021; 94:108749. doi:10.1016/j.jnutbio.2021.108749

21. Saati GE, Archer MC. Inhibition of fatty acid synthase and Sp1 expression by 3,3'-diindolylmethane in human breast cancer cells. *Nutr Cancer*. 2011; 63(5):790-794. doi:10.1080/01635581.2011.570896

22. Thomson CA, Ho E, Strom MB. Chemopreventive properties of 3,3'-diindolylmethane in breast cancer: evidence from experimental and human

studies. *Nutr Rev*. 2016; 74(7):432-443. doi:10.1093/nutrit/nuw010

23. Nachshon-Kedmi M, Yannai S, Fares FA. Induction of apoptosis in human prostate cancer cell line, PC3, by 3,3'-diindolylmethane through the mitochondrial pathway. *Br J Cancer*. 2004; 91(7):1358-1363. doi:10.1038/sj.bjc.6602145

24. Fares F, Azzam N, Appel B, Fares B, Stein A. The potential efficacy of 3,3'-diindolylmethane in prevention of prostate cancer development. *Eur J Cancer Prev*. 2010; 19(3):199-203. doi:10.1097/CEJ.0b013e328333fbce

25. Nachshon-Kedmi M, Fares FA, Yannai S. Therapeutic activity of 3,3'-diindolylmethane on prostate cancer in an in vivo model. *Prostate*. 2004; 61(2):153-160. doi:10.1002/pros.20092

26. Kandala PK, Srivastava SK. Diindolylmethane suppresses ovarian cancer growth and potentiates the effect of cisplatin in tumor mouse model by targeting signal transducer and activator of transcription 3 (STAT3). *BMC Med*. 2012; 10:9. doi:10.1186/1741-7015-10-9

27. Kandala PK, Wright SE, Srivastava SK. Blocking epidermal growth factor receptor activation by 3,3'-diindolylmethane suppresses ovarian tumor growth in vitro and in vivo. *J Pharmacol Exp Ther*. 2012; 341(1):24-32. doi:10.1124/jpet.111.188706

***Citation:*** Pedro Jose Gonzalez-Matarín (2024), "**Effects of Diindolylmethane Supplementation in cáncer therapy: a narrative review**", Arch Lif Sci Nutr Res ; 8(1):1-6.

**DOI:** 10.31829/2765-8368/alsnr2024-8(1)-003