Middle Eastern Cancer and Oncology Journal (MECOJ)
ISSN: 3080-1427 (online) / 3080-1419 (print)
Volume 1, Issue 2 (April 2025 – June 2025), pp: 23-37

Review Article

Cancer Chemoprevention: An Exploration of the Efficacy and Potential of Various Materials (Synthetic and Natural)

Ikram Faza [1,2,a*], Leila Achour [1,2,b], Yosr Trabelsi [1,c], Hajer Felfel [3,d], Mounsef Freddy [4,e], Chema Drira [1,2,f]

[1] Departement of Pharmacy, Marrow Bone Transplant Center, Tunisia.
[2] University Tunis Manar, LR 18ES39, Tunis, Tunisia.
[3] University of Monastir, Faculty of Pharmacy of Monastir, Tunisia.
[4] Departement of Pharmacy, Hospital of Saint-Etienne, France.

E-mail: fazaa.ikram@hotmail.fr [a,*], leila.achourr@gmail.com [b], trabelsi.yosr93@gmail.com [c], hajerfalfel@yahoo.com [d], freddy.mounsef@chu-st-etienne.fr [e], chemadrira@gmail.com [f]

Received: 27 March 2025 | Revised: 07 May 2025 | Accepted: 23 May 2025 | Published: 09 June 2025

Abstract

The increasing incidence of cancer around the world has led to a growing focus on cancer chemoprevention in contemporary medical research. Chemoprevention, defined as the use of natural or synthetic bioactive substances to impede, delay, or mitigate tumor growth, is a critical component of cancer research and treatment. In light of the limitations of current chemotherapy, including toxicity and chemoresistance, which result in suboptimal success rates, the pursuit of safer and more effective alternatives has become imperative. The present study explores the efficacy of various natural and synthetic compounds as chemopreventive agents, drawing upon evidence from pre-clinical trials. This paper investigated the actions of chemopreventive drugs in obstructing cancer progression, with a specific emphasis on their role in safeguarding DNA integrity and suppressing the growth of premalignant cells. A comprehensive evaluation of pre-clinical trials was conducted to assess the practicality and advantages of using dietary components as chemopreventive agents.The trials reviewed provide substantial evidence supporting the potential of dietary components in cancer chemoprevention. These elements have demonstrated encouraging efficacy in impeding cancer progression by targeting DNA protection and constraining the proliferation of premalignant cells. Moreover, the implementation of these chemopreventive approaches in clinical trials has exhibited considerable promise, particularly in the protection of individuals at high risk of cancer development. The demonstrated efficacy of chemopreventive agents in diminishing cancer risk, especially in populations with heightened vulnerability, significantly reinforces their validity and potential utility. In light of the challenges associated with conventional chemotherapy, there is a growing recognition of the potential for a paradigm shift towards the integration of multiple chemopreventive compounds. This integration could represent a transformative phase in cancer treatment strategies.

Keywords: *Cancer Chemoprevention, Natural Compounds, Synthetic Compounds.*

*** Correspondence Author**

Cite This Article: Faza, I., Achour, L., Trabelsi, Y., Felfel, H., Freddy, M., & Drira, C. (2025). Cancer Chemoprevention: An Exploration of the Efficacy and Potential of Various Materials (Synthetic and Natural). *Middle Eastern Cancer and Oncology Journal*, *1*(2), 23–37. https://doi.org/10.61706/MECOJ160139

Introduction

Cancer Chemoprevention

The fundamental principle of cancer chemoprevention involves the utilization of bioactive agents, whether synthetic or natural, to impede, postpone, or halt tumor formation. Chemopreventive agents play a crucial role in forestalling further DNA damage and in inhibiting the proliferation of premalignant cells that have already sustained DNA damage. This, in turn, decelerates cancer progression. There is mounting empirical evidence supporting the use of dietary components as chemopreventive tools, which is further supported by a number of pre-clinical trials. In light of the global escalation in cancer diagnoses, which has given rise to profound health concerns, the limitations of prevailing chemotherapy regimens—most notably their toxicity and the issue of chemoresistance—have brought to the fore the pressing need for more effective and safer therapeutic alternatives. The strategy of increasing the intake of fruits and vegetables, owing to their rich phytochemical content, emerges as a straightforward yet potent method to reduce cancer incidence. This approach is further substantiated by the demonstrated efficacy of chemopreventive drugs in protecting populations at elevated risk of cancer. Indeed, this tactic has demonstrated its efficacy across a range of clinical trials focused on cancer management (G. et al., 2022; Jackson & Chester, 2015; Ranjan et al., 2019; Russo et al., 2010).

Breast Cancers

Breast cancer, with approximately 2 million new cases annually and an estimated 500,000 deaths, is a significant global health concern. The disease encompasses various histotypes and molecular subtypes, each characterized by distinct etiology, risk factors, treatment responses, and prognoses. It is noteworthy that approximately 75% of breast cancer diagnoses are made in postmenopausal women, while a smaller percentage (5–7%) occurs in women under 40 years old in high-income countries (Pashayan et al., 2020).

General Preventive Strategies for Breast Cancers

A paradigm shift has occurred, with breast tumors now eclipsing cardiovascular disease as the foremost cause of mortality in countries with advanced healthcare systems. Although clinical markers such as blood pressure and serum cholesterol levels have been utilized for a considerable period to direct preventative measures in cardiovascular disease, the application of analogous principles to cancer has only recently become viable (Pashayan et al., 2020). In the field of oncology, the utilization of emerging biomarkers, including circulating tumor DNA (ctDNA), hormone receptor status, and BRCA1/2 mutation testing, has witnessed a marked increase in recent practice. These biomarkers play a crucial role in the stratification of cancer risk and the formulation of preventive strategies. The primary objective of breast cancer prevention entails the avoidance of well-established risk factors, including hormone replacement therapies that contain progesterone. Additionally, adopting healthier lifestyle habits, such as reducing alcohol consumption and maintaining a healthy body weight, is crucial. Notwithstanding these measures, numerous risk factors for breast cancer, such as family history and genetic predisposition, remain unmodifiable. However, several interventions have demonstrated an impact on breast cancer risk (Pashayan et al., 2020).

Chemoprevention with an Anti-Estrogen Strategy

A body of evidence suggests a decline in the incidence of hormone receptor-positive subtypes of breast malignancies, as evidenced by randomized controlled trials (RCTs) focusing on primary prevention with selective estrogen receptor modulators or aromatase inhibitors. A study of a 20-year daily tamoxifen usage regimen has demonstrated a substantial decrease in breast cancer risk. Notwithstanding a substantial decline in breast cancer incidence, clinical trials have not exhibited a concomitant enhancement in overall or breast cancer-specific survival. This phenomenon may be attributed to the relatively low baseline mortality rate in screened populations and the efficacy of treatment after diagnosis, which reduces the observable mortality benefit from preventive use. Consequently, it remains challenging to justify anti-estrogen therapy for healthy women over reserving it for adjuvant settings (Pashayan et al., 2020). Jack and his colleague conducted a randomized controlled trial from April 14, 1992, to March 30, 2001. During this period, 7,154 eligible women were enrolled from genetics and breast care clinics across eight countries. Participants were randomly divided into two groups: 3,579 received tamoxifen, and 3,575 were given a placebo. Following a median follow-up period of 16 years, a total of 601 cases of breast cancer were documented. Specifically, 251 cases (7.0%) occurred in the tamoxifen group (n = 3,579), and 350 cases (9.8%) occurred in the placebo group (n = 3,575). The hazard ratio for the tamoxifen group was determined to be 0.71 (95% CI: 0.60-0.83), with a statistically significant p-value of <0.0001. These findings indicate that tamoxifen provides sustained protection following treatment discontinuation, thereby markedly enhancing the benefit-risk ratio for breast cancer prevention (Cuzick et al., 2015).

Surgical Prevention Strategy

In women with a hereditary pathogenic BRCA1/2 mutation, comprising approximately 3% of the

population, prophylactic bilateral mastectomy is the most effective method to prevent breast tumors and lower cancer-specific mortality. The extant evidence does not suggest that nipple-sparing mastectomies compromise the effectiveness of risk reduction in these women. Common complications include wound dehiscence, infection, implant loss or flap necrosis, asymmetry, and capsular contracture (Pashayan et al., 2020). The overall complication rate for nipple-sparing mastectomies is 22.3%, with a 5.9% rate of nipple necrosis. However, beyond physical complications, surgery can entail unintended psychological impacts, such as emotional distress related to altered body image, and practical considerations. Consequently, a comprehensive evaluation of clinical utility, feasibility, and acceptability is imperative to ascertain an acceptable risk level for surgical intervention (Pashayan et al., 2020).

Curcumin as Chemopreventive for Breast Tumors

D. Liu & Chen (2013) have indicated the vulnerability of specific aggressive and recurrent cancers to the chemopreventive and antitumoral effects of curcumin. This compound has been demonstrated to modulate the expression and activity of a broad spectrum of proteins, including inflammatory cytokines, enzymes, transcription factors, and genes related to cell survival and proliferation. Furthermore, curcumin has been shown to mitigate the toxicity of mitomycin C (D. Liu & Chen, 2013). Notwithstanding its notable antineoplastic properties, curcumin confronts significant obstacles due to its water insolubility and inherent instability. The application of rubusoside, a solubilizing agent, has the potential to enhance the solubility of curcumin. Moreover, the chemopreventive and chemotherapeutic efficacy of curcumin may be enhanced by targeted delivery to tumor sites, achieved through synthetic analogues or nanotechnology-based formulations (D. Liu & Chen, 2013).

Song et al. (2018) have discussed the anticancer properties of curcumin, attributing them to its capacity to inhibit pro-cancer activities such as inflammation, angiogenesis, and metastasis, while promoting apoptosis in cancer cells. Specifically, curcumin has been shown to suppress several key signaling pathways that are integral to cancer development and therapy, including p53, Ras, phosphatidylinositol-3- kinase, protein kinase B, Wnt-catenin, and the mammalian target of rapamycin. A substantial body of clinical research has demonstrated the potential of curcumin, when used in isolation or in conjunction with other pharmaceutical agents, to exhibit anticancer effects, particularly in the context of breast cancer treatment (Song et al., 2018).

Genistein and Resveratrol as Breast Cancers chemoprevention

Genistein, a soy derivative, and resveratrol, a phytoalexin present in red grapes and red wine, are two dietary polyphenols that have garnered significant interest from the health and research communities due to their potential implications in breast cancer prevention. Research conducted by Whitsett Jr. & Lamartiniere (2006) has demonstrated that both genistein and resveratrol possess the capacity to impede the progression of breast cancer in animal models (Whitsett Jr. & Lamartiniere, 2006).

The temporal parameters of genistein exposure are of paramount importance for its protective effects on the mammary glands. In the context of early-life exposure, genistein has been demonstrated to be associated with an increased differentiation of mammary glands, alterations in cell proliferation and apoptosis, and the activation of tumor-suppressor genes. These changes contribute to its protective role against breast cancer (Whitsett Jr & Lamartiniere, 2006).

Conversely, the beneficial effects of dietary resveratrol are believed to stem from its impact on cell proliferation and death within the terminal ductal structures of the mammary gland. Collectively, genistein and resveratrol exert their anti-carcinogenic influence in the breast by modulating critical pathways involved in mammary gland development and differentiation (Whitsett Jr & Lamartiniere, 2006).

Lung Cancers

Lung tumors persist as a predominant oncological challenge, distinguished by their elevated incidence and mortality rates in comparison to other tumor types. The classification of lung cancer is typically divided into two primary categories: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all diagnosed cases. It is important to note that lung malignancy is the leading cause of cancer-related mortality among males, surpassing all other types. Furthermore, it accounts for a greater proportion of female cancer-related deaths than any individual tumor type, underscoring its significant impact on global health (Cortés-Jofré et al., 2020).

General Lung Tumors Prevention

The prevention of lung tumors encompasses both primary and secondary measures. The primary objective of primary prevention is the implementation of tobacco control policies, with initiatives that are designed to impede smoking initiation and facilitate cessation among individuals who currently smoke. Secondary prevention is defined as the implementation of early detection and intervention programs specifically for lung malignancies. In recent decades, a multitude of

international trials have evaluated the effectiveness of low-dose computed tomography (LDCT) as a screening tool for lung tumors. Pivotal studies, including the National Lung Screening Trial (NLST) in the United States and the European Lung Cancer Screening (NELSON) trial, have demonstrated that lung-cancer mortality among high-risk populations is significantly reduced by LDCT screening. In contrast, earlier approaches, such as chest X-rays and sputum cytology, have been deemed ineffective in reducing lung malignancies mortality (Bonney et al., 2022; Cui et al., 2015; Lung Cancer Prevention (PDQ®) - NCI - –Health Professional Version, 2025).

The role of chemoprevention in lung tumors remains an active area of research. Chemoprevention is defined as the use of natural or synthetic agents to inhibit, reverse, or prevent the process of carcinogenesis before the development of invasive malignancy. A series of investigations have been conducted to assess the potential of micronutrients, such as beta-carotene and vitamin E, in the prevention of lung cancer (Gold et al., 2012). However, the available evidence remains inconclusive regarding the efficacy of beta-carotene in non-smokers for reducing lung malignancies risk or mortality. Notably, studies indicate that high-dose beta-carotene supplementation may increase the risk of lung cancer development and mortality in heavy smokers. In a similar vein, the impact of vitamin E supplementation on lung tumor risk has not been demonstrated to be statistically significant (Lung Cancer Prevention (PDQ®) - NCI - –Health Professional Version, 2025).

Chemopreventive Drugs for Lung Malignancies

Pioglitazone

The chemopreventive efficacy of pioglitazone, a peroxisome proliferator-activated receptor (PPAR) inhibitor, has been explored in animal models of lung malignancies. In a particular study, the administration of pioglitazone to p53 wild-type mice occurred eight weeks after exposure to the vinyl carbamate carcinogen. The result was a significant 64% reduction in tumor incidence in a lung tumor model. In addition, pioglitazone exhibited the capacity to hinder the development of tumors in mice harboring a p53 mutation (p53wt/Ala135Val). A series of studies have demonstrated that pioglitazone has the potential to reduce the incidence of lung malignancies induced by benzo(a)pyrene by 63%. Furthermore, the combination of pioglitazone and budesonide, an anti-inflammatory drug, was found to significantly reduce tumor burden by 90% (G. et al., 2022; Keith et al., 2019).

Grape seed Procyanidine Extract

Procyanidins, which are derived from grape seeds, have exhibited significant anti-lung malignancy efficacy in both in vitro and in vivo studies. It is noteworthy that the administration of procyanidins at varying dosages exhibited a substantial inhibitory effect on the growth of A549 and H1299 lung tumor xenografts. This reduction in tumor growth was associated with an increased expression of the insulin-like growth factor receptor within the tumor microenvironment. Subsequent research has revealed a novel mechanism underlying the antineoplastic effects of procyanidins on lung malignant cells: the downregulation of MicroRNA-19a/b. Furthermore, a subsequent study revealed that oral administration of Leucoselect phytosome, a formulation of procyanidins, effectively inhibited the growth of A549 xenografts (G. et al., 2022; Mao et al., 2019).

2-Phenethylisothiocynate

Cruciferous vegetables contain bioactive compounds, such as 2-phenethylisothiocyanate (PEITC), which exhibit notable anti-carcinogenic properties. PEITC has been identified as a potential inhibitor of cytochrome P450 enzymes, which play a crucial role in the metabolism of various carcinogens. In addition, this compound has demonstrated the capacity to impede the action of 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a tobacco-specific carcinogen that has gained notoriety due to its prevalence in tobacco products. Research has demonstrated that PEITC has the capacity to result in a 50% reduction in NNK-induced lung tumors and can impede NNK-induced DNA methylation. However, it is noteworthy that liver and oral cavity tumors induced by NNK appeared to be resistant to the suppressive effects of PEITC (G. et al., 2022; Gupta et al., 2014).

Curcumin

Recent studies have identified curcumin as a potential chemopreventive agent against nicotine-induced survival signaling in lung cancer cells. A substantial body of research has demonstrated that the phenomenon in question disrupts these survival signals through mechanisms that are independent of the p53 pathway. In addition, curcumin's efficacy as a chemopreventive agent has been demonstrated in Swiss albino mice models. The findings have demonstrated notable preventive effects against lung carcinogenesis induced by benzo[a]pyrene (B(a)P), a recognized environmental carcinogen commonly found in cigarette smoke and deep-fried foods. These findings suggest the potential of curcumin as a therapeutic agent in mitigating lung tumor risk, particularly in the context of exposure to specific environmental carcinogens (G. et al., 2022; Yang et al., 2022).

Colorectal Cancers

Colorectal cancers (CRCs) are a major global health concern, with mortality rates of 9.2%, second only to lung cancer in terms of mortality rates. Furthermore, CRCs account for 6.1% of all tumors

diagnosed. Projections indicate a substantial increase in mortality from rectal and colon malignancies, with an expected rise of 60% and 71.5%, respectively, by 2035. These variations in incidence and mortality rates are often correlated with a country's level of economic development, making CRCs' prevalence a potential indicator of economic status. Furthermore, lifestyle factors, including body fat levels and dietary habits, play a crucial role in the escalating morbidity rates associated with CRCs (Sawicki et al., 2021).

The 1970s witnessed the emergence of the concept of chemoprevention as a strategy to reduce the incidence and mortality of cancer, including CRCs. A critical aspect of this approach is the identification of well-established biomarkers that can serve as credible endpoints in clinical chemoprevention trials. The development of chemopreventive strategies for CRCs has been hindered by the challenge of identifying reliable biomarkers. In recent years, the emergence of reliable biomarkers, including colorectal adenomas and aberrant crypt foci, has led to the initiation of chemoprevention trials targeting CRCs. This advancement has facilitated the development of agents that hold significant promise in the prevention of colorectal tumors (Umezawa et al., 2019).

Potential Chemopreventive Agents for Colorectal Cancers

Non-steroidal Anti-Inflammatory Drugs and Aspirin

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been the subject of extensive research as potential chemopreventive agents against CRCs. The protective effects of aspirin against CRCs were initially reported in 1988. Although the precise mechanism remains to be fully elucidated, it is generally accepted that NSAIDs exert their preventive effects by inhibiting cyclooxygenase-2 (COX-2). It is noteworthy that COX-2 is undetectable in normal gastrointestinal epithelium; however, it is present in over 80% of CRCs and 40% of colorectal adenomas. Clinical studies have demonstrated that the non-selective cyclooxygenase (COX) inhibitor sulindac can reduce both the number and size of colorectal adenomas (Maniewska & Jeżewska, 2021; Umezawa et al., 2019).

This understanding has led to the implementation of randomized controlled clinical trials (RCTs) investigating NSAIDs, particularly those designed to selectively inhibit COX-2. For instance, in the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial, the use of rofecoxib resulted in a 24% reduction in the risk of developing colorectal adenomas. Concurrently, the Adenoma Prevention with Celecoxib (APC) study determined that celecoxib diminished adenoma numbers in a dose-dependent manner (Maniewska & Jeżewska, 2021; Umezawa et al., 2019).

The collective findings of these studies underscore the protective effect of coxibs against the development of recurrent colorectal adenomas. Nevertheless, the utilization of coxibs as chemopreventive agents is a subject of controversy due to their substantial cardiovascular toxicity. The heightened risk of cardiovascular incidents observed in these trials—particularly myocardial infarction and other thrombotic complications—resulted in the premature cessation of both studies, as recommended by their respective data and safety monitoring boards (Maniewska & Jeżewska, 2021; Umezawa et al., 2019).

Metformin

Recent findings provide mounting evidence that metformin may possess antineoplastic properties beyond its recognized therapeutic application in the management of Type 2 diabetes. The anti-tumor mechanisms of metformin are primarily multifaceted. Initially, metformin exerts its effects indirectly through systemic metabolic changes, manifesting in reduced plasma glucose and insulin levels. Insulin, acting as a proliferative factor, has been shown to promote cell growth and inhibit apoptosis. This process is achieved by downregulating the expression of insulin-like growth factor-binding protein (IGFBP), thereby augmenting the production of insulin-like growth factor 1 (IGF1). The second mechanism pertains directly to tumor cells, predominantly via the activation of AMP-activated protein kinase (AMPK). The AMPK/mTOR signaling axis plays a crucial role in this context by inhibiting protein synthesis and gluconeogenesis in tumor cells. This hypothesis is further substantiated by epidemiological studies that demonstrate a reduced incidence of cancer among metformin users. A recent meta-analysis has indicated a significantly reduced risk of colon neoplasia in Type 2 diabetes patients treated with metformin (Umezawa et al., 2019; Xiao et al., 2022).

A recent randomized controlled trial (RCT) assessed metformin's efficacy in a non-diabetic cohort, marking a notable advancement in the field. The study revealed a 40% reduction in adenoma incidence and a 33% decrease in the overall count of colon polyps in participants administered low-dose metformin over a one-year period following polypectomy. These findings suggest that the anti-cancer effects of metformin may extend beyond its impact on Type 2 diabetes management (Umezawa et al., 2019; Xiao et al., 2022).

Omega-3 Polyunsaturated Fatty Acids and Colorectal Cancers Risk

The relationship between fish consumption, a primary source of marine n-3 polyunsaturated fatty acids (PUFAs), and colorectal malignancies risk has been the subject of extensive research, yielding mixed outcomes. Observational studies have identified an

inverse correlation between PUFA intake and the risk of colon tumor, particularly in distal regions of the large bowel. A notable meta-analysis suggests a 12% reduction in colorectal malignancy risk among individuals who regularly consume fish. The antineoplastic mechanisms of Omega-3 PUFAs, while not fully elucidated, are believed to involve several pathways: (i) inhibition of cyclooxygenase activity, (ii) generation of novel anti-inflammatory lipid mediators, (iii) direct signaling via G protein-coupled receptors by fatty acids, (iv) modifications in membrane dynamics affecting cell surface receptor functionality, and (v) induction of cellular oxidative stress (Lee et al., 2017; Umezawa et al., 2019).

Notwithstanding the aforementioned proposed mechanisms, there is a conspicuous paucity of interventional trials that have yielded definitive evidence. However, a recent randomized controlled trial focusing on dietary advice to increase omega-3 PUFA intake showed a trend toward decreased colorectal tumor incidence in patients post-polypectomy over a 24-month period, although these findings require further substantiation (Lee et al., 2017; Umezawa et al., 2019).

Calcium and Vitamin D: Implications for Colorectal Cancers Prevention

Extensive observational studies have established an association between dietary calcium intake and a reduced risk of colon adenomas and CRCs. The proposed protective mechanism of dietary calcium involves its capacity to bind with secondary bile acids and ionized fatty acids in the colon lumen, forming insoluble complexes that are often referred to as "soaps." This binding process has the potential to mitigate the carcinogenic properties of these acids. Furthermore, calcium plays a critical role at the cellular level, inhibiting proliferation, encouraging differentiation, and inducing apoptosis in colon epithelial cells (Cruz-Pierard et al., 2022; Umezawa et al., 2019).

In addition to calcium, vitamin D has been implicated in colorectal cancer prevention. The active form of vitamin D, calcitriol, has been shown to possess antitumor properties by regulating gene expression, cell growth, and apoptosis. The present study hypothesizes that vitamin D, often working in synergy with calcium, may exert a protective effect against the development of colorectal cancers (CRCs). However, the precise mechanisms and the optimal levels of calcium and vitamin D intake for cancer prevention remain subjects of ongoing research (Cruz-Pierard et al., 2022; Umezawa et al., 2019).

However, further investigation through controlled interventional studies is necessary to definitively establish the role of calcium and vitamin D in colorectal tumor prevention and to determine the effective dosages for risk reduction (Cruz-Pierard et al., 2022; Umezawa et al., 2019).

Liver Cancers

Liver tumors present significant health concerns, with treatment options varying based on the disease's stage. Hepatocellular carcinoma (HCC) is the most prevalent form of liver malignancy, accounting for approximately 75% of all cases. The limitations imposed by the toxicities and other serious side effects of current first- and second-line medicines serve to curtail their usefulness in disease management (A. K. Singh et al., 2023). As demonstrated in recent literature, there are currently widely available agents used to reduce the rate of incidence of liver cancer (**Table 1**).

Table 1. Agents Used as Liver Cancer Chemoprevention

Chemotherapy for Liver Cancers	Summary	Clinical Evidence
Statin	Statins have been shown to consistently exhibit chemopreventive benefits in reducing the risk of hepatocellular carcinoma (HCC), with a dose-response relationship being observed in the majority of studies. A significant decrease in risk was observed for each 50 cumulative defined daily doses (cDDD) added to the annual total statin dose (Goh & Sinn, 2022).	Two-stage dose- response meta-analysis and separate series of dose-response meta- analyses
Aspirin	Aspirin has been demonstrated to have potential in the attenuation of T-cell-driven inflammation and the impediment of hepatocellular carcinoma (HCC) progression in specific mouse models. The ingestion of low-dose aspirin over a period of three to twelve months has been shown to be associated with a reduced risk of hepatocellular carcinoma (HCC). Prolonged usage, especially beyond five years, has been associated with a considerable reduction in HCC incidence and mortality rates (Abdelmalak et al., 2023; Goh & Sinn, 2022).	Mouse model experiments and Swedish cohort study
Metformin	The administration of metformin has been demonstrated to result in a significant decrease in the incidence of hepatocellular carcinoma (HCC) and mortality due to liver disease. The observed effects are believed to be the result of a reduction in plasma insulin levels, as well as indirect mechanisms involving apoptosis, immune system activation, and the activation of AMP-activated protein kinase (AMPK) (Cunha et al., 2020; Marchesini et al., 2001).	Case-control study and various supporting studies
Resveratrol	Resveratrol, a polyphenol found in red grapes, has been shown to possess antioxidant and anti-inflammatory properties. The study demonstrated the efficacy of the treatment in managing non-alcoholic fatty liver disease (NAFLD) and promoting apoptosis in hepatocellular carcinoma (HCC) cells. Furthermore, in vitro studies have demonstrated that resveratrol can enhance the anti-proliferative effects of sorafenib on aerobic glycolytic HCC cells by modulating the PI3K/Akt/mTOR signaling pathway. This synergistic interaction enhances apoptosis and inhibits cell cycle progression, offering potential for combination strategies in hepatocellular carcinoma therapy (Abdel-Hamid et al., 2018; Baur & Sinclair, 2006; Bujanda et al., 2008; SHANG et al., 2008; G.-L. Wang et al., 2009; Xin et al., 2013).	Studies on NAFLD management and effects on HCC cells
Ginger	Ginger has been demonstrated to possess a chemopreventive effect against liver tumors in a rat model. The administration of dosages of 75 mg/kg, 150 mg/kg, and 300 mg/kg on a daily basis resulted in a reduction of dyschromatic nodules, positive focal regions, and oxidative stress markers. However, the evidence from human studies remains limited, and further clinical trials are necessary to validate the safety and efficacy of ginger as a chemopreventive agent for liver cancer in humans. Ginger has been shown to impede cell proliferation and promote apoptosis, thereby reducing oxidative and inflammatory damage to the liver (Ali et al., 2008; Hamza et al., 2021).	Rat model study on liver cancers induced by Diethylnitrosamine and 2- acetylaminofluorene

Ovarian Tumors

The mortality rate associated with ovarian cancers (OvCas) remains the highest among gynecological malignancies, with approximately 46% of patients surviving beyond five years post-diagnosis. This statistic highlights the critical importance of OvCas chemoprevention as a strategic intervention in combating this formidable disease (Xiao et al., 2022). Despite extensive research efforts, the establishment of optimal chemoprevention strategies for OvCas has remained elusive, presenting a persistent challenge in clinical practice. However, seminal observations

indicating that oral contraceptives may offer a protective effect against this malignancy have provided substantial evidence, or perhaps a proof-of-concept, underscoring the potential efficacy of chemopreventive approaches in OvCas management (Kathawala et al., 2018). In addition to oral contraceptives, other chemopreventive agents are employed to reduce the risk of ovarian cancer (**Table 2**).

Table 2. Agents Used as Ovarian Cancers Chemoprevention

Chemoprevention Agents for Ovarian Cancer	Summary	Clinical Evidence
Oral Contraceptives	Extensive research supports a 30% reduction in ovarian cancer incidence with oral contraceptive use, and a dose-response relationship is observed with extended duration. Even high-risk groups, such as those with a history of BRCA1/2 mutations, have demonstrated a reduction in risk (Kathawala et al., 2018; Schrijver et al., 2021).	Pivotal study and meta- analysis of 55 studies
NSAIDs	A body of research has emerged that suggests a potential benefit of NSAIDs, particularly aspirin, in the reduction of ovarian cancer risk. However, contrasting findings exist regarding their association with ovarian and endometrial malignancies. The extant literature on the subject is inconclusive, with some studies suggesting a reduced risk and others failing to establish a definitive link (Bonovas et al., 2005; Kathawala et al., 2018; Trabert et al., 2019).	Human interventional studies and meta-analysis
Retinoids	Retinoids, including vitamin A derivatives, have demonstrated potential in the prevention of ovarian malignancies. Cellular retinol-binding protein-1 (CRBP-1) loss has been implicated in ovarian cancer, and retinoids have been shown to influence apoptosis and gene regulation (Hunsu et al., 2021; Kathawala et al., 2018).	Role of Retinoids in biological processes
Natural Compounds	Plant-derived compounds, such as flavonoids and curcumin, have demonstrated potential in the inhibition of ovarian cancer cell proliferation and the induction of apoptosis. Curcumin, in particular, has demonstrated chemopreventive and antitumor properties in reducing ovarian tumor incidence and progression (Kathawala et al., 2018).	Curcumin's effects on hen model and molecular analysis (Sahin et al., 2018)

Bladder Tumors

In the domain of urinary system malignancies, bladder cancers (BCs) are the most prevalent, as indicated by their preeminent ranking (Choi & Roberts, 2016). This prevalence underscores the imperative need for advancements in both chemoprevention and treatment modalities for BCs. A body of research in the epidemiological field indicates that maintaining adequate levels of vitamin A in the diet may serve as a protective factor against the development of breast malignancies. In light of their robust antioxidant characteristics and their capacity to regulate cellular processes, including proliferation, differentiation, and apoptosis, retinoids—both natural and synthetic derivatives of vitamin A—have emerged as a pivotal area of inquiry in the realm of oncological research (Dobruch & Oszczudłowski, 2021).

Chemopreventive Methods Currently in Use for Bladder Malignancies Various Vitamins

A substantial body of research has previously investigated the roles of vitamins C, B6, E, and the essential trace element selenium. Despite the numerous studies conducted on chemoprevention in bladder cancers (BCs), identifying an efficacious compound remains elusive. Among the agents that were investigated, retinoids—derivatives of vitamin A—and alpha-tocopherol—a form of vitamin E—were considered for their potential in bladder tumor prevention. In vitro studies have demonstrated that vitamin A supplementation could inhibit bladder cancer development in rats predisposed to such malignancies due to exposure to environmental carcinogens (Leone et al., 2017; Tratnjek et al., 2021).

However, there is an absence of clinical evidence that definitively demonstrates the chemopreventive efficacy of retinoids. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, a randomized controlled trial, enrolled high-risk smokers and assigned them to receive beta-carotene, alpha-tocopherol, both, or a placebo. The study's primary outcome was the development of bladder malignancies, and it found no protective effect of the compounds against this specific type of cancer. A secondary analysis of the SELECT trial found no protective benefits of vitamin E and selenium against BCs (Leone et al., 2017; Tratnjek et al., 2021).

In addition, investigations examining the potential of retinoids for secondary chemoprevention have not yielded conclusive results. One trial was prematurely halted due to concerns regarding toxicity (elevated risk of myocardial infarction) and an absence of discernible benefits.

Statins and Metformin for Chemoprevention of Hepatocellular Carcinoma Moreover, two randomized trials examining the efficacy of pyridoxine (B6) for secondary chemoprevention yielded no positive outcomes. The preventive effects of ascorbic acid (vitamin C) have not been definitively confirmed in controlled studies, and the evidence from epidemiological research is inconclusive. Despite the evidence from epidemiological and clinical studies suggesting a potential role for chemoprevention, megadoze multivitamins have yet to demonstrate therapeutic efficacy. A study was conducted to investigate the effectiveness of statins and metformin in preventing hepatocellular carcinoma.

NSAIDS and Cox-2 Inhibitors as Chemoprevention of Bladder Tumors

Remarkably, an in vitro study employed allyl isothiocyanate (AITC) and celecoxib to target prostaglandin E2, a principal downstream effector of Cox-2. This approach also involved the activation of caspases and a reduction in the expression of vascular endothelial growth factor in tumor tissues. These outcomes suggest that the combined use of AITC and celecoxib may result in a synergistic effect in the prevention of bladder cancer. The findings, which hold considerable promise, necessitate further validation through preclinical studies in animal models (Daugherty et al., 2011; Leone et al., 2017).

Metformin as a Chemoprevention for Bladder Malignancies

In recent years, the potential anticancer properties of metformin have garnered considerable attention. A substantial body of research has demonstrated the efficacy of this substance in reducing the risk of various types of cancers, including breast, prostate, colon, pancreatic, and bladder malignancies. The mechanisms underlying metformin's anticancer effects can be categorized into two primary classifications: those that are directly related to insulin modulation and those that are insulin-independent (i.e., direct versus indirect anticancer pathways). The direct pathway is characterized by the activation of AMP-activated protein kinase (AMPK) and the inhibition of the mammalian target of rapamycin (mTOR). It is important to note that AMPK activation also plays a pivotal role in the indirect pathway. Metformin has been demonstrated to disrupt gene transcription associated with hepatic glucose production, thereby reducing glucose synthesis, enhancing muscle glycogen breakdown, and consequently leading to decreased levels of insulin and serum glucose (C.-Q. Liu et al., 2022).

Skin Cancers

On a global scale, cutaneous neoplasms constitute a substantial cause of mortality and morbidity. Factors such as excessive sun exposure, chemical exposure, and infection with certain viruses have been demonstrated to compromise the immune system, thereby contributing to the onset of skin cancers and other severe dermatological conditions. These factors play distinct roles in the initiation, promotion, and progression of the process of skin carcinogenesis. Presently, the employment of natural product interventions signifies a flourishing and profoundly auspicious strategy within the domain of cancer chemoprevention. Such interventions are increasingly recognized for their potential to prevent, arrest, or reverse the carcinogenic process (M. Singh et al., 2014; Tow et al., 2023).

Nicotinamide as a Skin Tumors Chemoprevention Agent

The photoprotective properties of vitamin B3 (nicotinamide) encompass a spectrum of beneficial effects, including enhanced DNA repair, attenuation of skin immune response suppression due to ultraviolet (UV) radiation, modulation of inflammatory cytokine production, improvement in skin barrier functionality, and replenishment of cellular energy levels post-UV exposure. It has been demonstrated that the administration of nicotinamide at pharmacological doses to individuals at high risk can reduce the incidence of actinic keratoses and non-melanoma skin tumors. This positions nicotinamide as a viable, accessible, and cost-effective chemopreventive agent, offering significant clinical utility (Jiminez & Yusuf, 2023; Tow et al., 2023).

Non-Steroidal Anti-Inflammatory Drugs (NASIDs) as Skin Cancers Chemoprevention Agents

Cyclooxygenase-2 (COX-2) and its metabolic product, prostaglandin E2 (PGE2), have been shown to play pivotal roles in the inflammation and carcinogenesis of the skin. A substantial body of research has examined the anti-inflammatory effects of nonsteroidal anti-inflammatory drugs (NSAIDs), which are accomplished through the selective or non-selective inhibition of cyclooxygenase-2 (COX-2) and the subsequent decrease in prostaglandin E2 (PGE2) synthesis. The hypothesis posits that the anti-inflammatory efficacy of NSAIDs is predominantly attributed to COX-2 inhibition, while COX-1 inhibition is linked to gastrointestinal toxicity. Consequently, a variety of COX-2 selective inhibitors, including celecoxib, have been developed to diminish or eliminate this adverse effect. Consequently, selective COX-2 inhibitors emerge as promising candidates for chemoprevention. However, despite the presence of encouraging data, clinical studies have yet to provide unequivocal support for the utilization of NSAIDs as chemopreventive agents for skin tumors (Jiminez & Yusuf, 2023; Tow et al., 2023).

Retinoids as Skin Malignancies Chemoprevention Agents

Retinol, more commonly referred to as vitamin A, was discovered in the early 20th century and has since been identified as a critical component for human health. Subsequent in-depth biochemical investigations have identified the retinoid signaling pathway as a promising therapeutic avenue in oncology. Retinoids have been demonstrated to play a pivotal role in regulating key cellular processes, including proliferation, differentiation, and apoptosis. The utility of these cells has been thoroughly investigated in both prophylactic and therapeutic contexts across a range of solid tumors and hematological malignancies. Decades of rigorous research have led to the widespread acceptance of retinoids as a fundamental component of dermatological practice, with numerous studies demonstrating their efficacy in the treatment of various skin malignancies. Nevertheless, the guidelines for their utilization in skin cancer therapy are undergoing continuous refinement in response to emerging research findings. While retinoids are widely recognized for their versatility and effectiveness in dermatological applications, there remain several challenges and limitations in their use for the prevention and treatment of skin cancers (Ramchatesingh et al., 2022; Tow et al., 2023).

5-Fluorouracil as a Skin Tumors Chemoprevention Agent

The pharmacological action of 5-fluorouracil (5-FU) is characterized by its ability to inhibit thymidylate synthase, a key enzyme in the de novo synthesis of purines and pyrimidines. In addition to its direct inhibitory effect on this enzyme, 5-FU has been observed to incorporate its metabolites into RNA and DNA structures, thereby impacting cellular processes involved in transcription and replication. This mechanism has led to its proposition as a therapeutic agent for actinic keratosis and specific basal cell carcinoma variants. A notable clinical trial has validated the efficacy of topical 5-FU in hindering the progression of squamous cell carcinomas, highlighting its potential in chemoprevention (Bujanda et al., 2008; SHANG et al., 2008). However, when considering the oral formulation of 5-FU, its application as a chemopreventive agent for skin cancers encounters limitations. This is primarily attributable to the severe adverse drug reactions associated with this route of administration, which have constrained the feasible duration of chemoprevention in numerous patients (Tow et al., 2023).

Difluoromethylornithine

Enhanced polyamine synthesis has been identified as a hallmark of UV-induced skin cancers. Difluoromethylornithine (DFMO), an inhibitor of the enzyme ornithine decarboxylase, presents a potential intervention to counteract this process. Systemic administration of DFMO has been the subject of numerous clinical trials, investigating its solo efficacy and synergistic potential when combined with other treatments for the prevention of skin cancers. Although DFMO has demonstrated encouraging therapeutic benefits, its systemic use is not without drawbacks, including auditory side effects such as hearing loss. Consequently, the topical application of DFMO has been explored as a means to circumvent these systemic effects (Tow et al., 2023). The chemopreventive efficacy of DFMO has been substantiated in various clinical trials. A notable randomized, placebo-controlled phase IIb trial observed a reduction in skin polyamine concentrations and actinic keratoses (AKs) in patients with a minimum of ten AKs on their forearms following DFMO treatment. Another phase II study reported that topical DFMO application not only reduced AK counts but also inhibited polyamine synthesis and decreased p53 protein levels. Furthermore, the combination of DFMO with the anti-inflammatory nonsteroidal anti-inflammatory drug (NSAID) diclofenac has demonstrated potential in the prevention of squamous cell carcinoma (Jiminez & Yusuf, 2023).

Polyunsaturated Fatty Acids

Recent research has centered on the assessment of the efficacy of omega-3 polyunsaturated fatty acids (PUFAs) in mitigating sun-induced photoimmunosuppression. In a study involving 79 healthy women aged between 18 and 60, participants were randomly assigned to receive either a placebo lipid supplement or an omega-3 PUFA supplement, composed of 70% eicosapentaenoic acid (EPA) and 10% docosahexaenoic acid (DHA). To evaluate changes in photo immunosuppression, the study employed nickel contact hypersensitivity patches. Nickel was applied to skin areas exposed to 3.8 J/cm² of solar-simulated radiation (SSR) over a period of three days, in conjunction with three control sites that received either a placebo or PUFA supplements. The findings indicated a substantial decrease in photoimmunosuppression, as demonstrated by the responses to nickel contact hypersensitivity, in the group receiving omega-3 PUFAs. This outcome suggests a potential role for omega-3 PUFAs in enhancing skin protection against solar radiation and reducing the risk of skin tumors. This study is particularly pertinent in light of the documented ineffectiveness of conventional sunscreens in preventing photoimmunosuppression and UV-induced erythema. These factors contribute to the misuse and inadequate application of sunscreens, underscoring the need for improved sunscreen formulations. However, further human studies are necessary to fully establish the protective effects of PUFAs (Jiminez & Yusuf, 2023; Minokawa et al., 2021; Tow et al., 2023).

Phytochemicals: Epigallocatechin-3-Gallate (EGCG) Trials

Epigallocatechin-3-gallate (EGCG), the predominant polyphenol in green tea, is recognized for its potent antioxidant properties. In contrast to other chemopreventive agents that predominantly target the cyclooxygenase (COX) and lipoxygenase (LOX) pathways, EGCG's anti-inflammatory effects may be attributable to a distinct mechanism of action (Jiminez & Yusuf, 2023). Notwithstanding its potential, there is a conspicuous absence of clinical trials assessing the therapeutic efficacy and chemopreventive capabilities of EGCG. A singular human study indicated that green tea polyphenols could prevent UV-induced erythema in humans. However, a recent double-blind clinical study involving 50 healthy adults who supplemented their diets with green tea extract and vitamin C observed no significant reduction in skin erythema or leukocyte infiltration (Jiménez & Yusuf, 2023).

Furthermore, the chemopreventive effectiveness of EGCG was specifically assessed in a 12-week, double-blind clinical trial involving 51 participants with actinic keratoses (AK). The present study found no significant

differences in the prevention of nonmelanoma skin cancers (NMSCs) between the EGCG treatment and placebo groups, which may be attributable to poor absorption or inefficacy of the formulation. Recent research has explored strategies to enhance EGCG bioavailability, including the use of nanoemulsion systems, lipid-based carriers, and prodrug development to overcome its limited systemic exposure (Jiminez & Yusuf, 2023). Conversely, EGCG has exhibited notable efficacy in the treatment of melanoma skin cancer. The drug has been shown to inhibit cell proliferation, migration, and invasion by targeting E3 ubiquitin ligase. In both in vivo and in vitro settings, EGCG has been shown to reduce the association between TRAF6-UBC13(E2) and to decrease the activity of TRAF6 E3 ubiquitin ligase (Zhang et al., 2016). These findings suggest that EGCG may have a role as a chemopreventive agent for skin melanoma.

Prostate Cancers

In 2018, prostate tumors were estimated to account for approximately 1.28 million fatalities worldwide, constituting the second most prevalent cause of tumor-related deaths among males. Current estimates indicate that approximately 1.3 million new cases of prostate cancer will be diagnosed within the year (MOKBEL et al., 2019). Given the high incidence rate, clinical unpredictability, and notable molecular heterogeneity of prostate tumors, they represent a prime candidate for the development and application of chemopreventive strategies (MOKBEL et al., 2019). The following section details the agents utilized in the chemoprevention of prostate cancer (**Table 3**).

Table 3. Agents Ased as Prostate Cancers Chemoprevention

Chemoprevention Agents for Prostate Cancer	Summary	Clinical Evidence
5-Alpha- Reductase Inhibitors (5ARIs)	Finasteride and dutasteride have been demonstrated to be efficacious in the prevention of prostate malignancies. Notwithstanding the occurrence of adverse effects, the FDA has authorized their utilization. Observations of males with congenital 5-alpha-reductase deficiency support their potential utility (MOKBEL et al., 2019; Rivero et al., 2018).	Recent clinical trials
Vitamin E and Selenium	The SELECT trial (2001) investigated the potential of selenium, vitamin E, and their combination in the prevention of prostate cancer. Concerns regarding the efficacy of selenium dosages, as well as its potential implications for diabetes risk, have emerged. A slight increase in prostate cancer incidence was observed in the vitamin E cohort, contrary to prior expectations (Ledesma et al., 2011; MOKBEL et al., 2019).	Selenium and Vitamin E Cancer Prevention Experiment (SELECT)
Lycopene	Lycopene, a carotenoid present in tomatoes, has been demonstrated to exhibit efficacy in reducing the incidence of prostate cancer. While its antioxidant properties contribute to its overall efficacy, its anticarcinogenic effects are multifaceted. The hypothesis regarding the protection of cellular macromolecules is that it is a mechanism (MOKBEL et al., 2019; Rivero et al., 2018).	Nutraceutical carotenoid
Soy	A correlation has been observed between diets in Asia that are abundant in soy and a reduced incidence of prostate cancer. Soy isoflavones, which function as phytoestrogens, have been demonstrated to possess chemopreventative properties with respect to prostate cancer. Genistein and daidzein have been shown to inhibit cancer cell proliferation through hormonal and non-hormonal activities, as evidenced by meta-analyses (Applegate et al., 2018; Rivero et al., 2018).	Soy isoflavones
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	There is a well-established correlation between persistent inflammation and the development of high-grade prostate cancers. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, which possess anti-inflammatory properties, inhibit cyclooxygenases (COX) enzymes, thereby reducing inflammation and prostaglandin production. The chemopreventive effects of these compounds have been demonstrated by experimental evidence (Rivero et al., 2018; Shang et al., 2018).	Inhibition of COX enzymes
Statins	Statins have been demonstrated to reduce prostate-specific antigen (PSA) levels and impede the proliferation of prostate cancer cells. While epidemiological evidence supports a reduced cancer risk, the exact protective mechanisms, whether lipid-related or non-lipid-related, remain unclear (Craig et al., 2022; Rivero et al., 2018).	Lowering PSA levels and in vitro inhibition

Gastric Cancers

Gastric tumors, with nearly one million new cases diagnosed annually, are the fifth most common malignant tumors and the third leading cause of cancer-related deaths globally (Shah & Peek, 2021). This underscores the substantial health burden posed by gastric tumors, emphasizing the necessity of prevention and early detection strategies. Early-stage gastric cancers, particularly when they have not yet extended into the submucosa, can often be effectively managed through surgical intervention (Shah & Peek, 2021). However, in many countries, with the exception of a few where endoscopic screening is routinely conducted, gastric tumors are predominantly diagnosed at advanced stages, typically when symptoms become noticeable. Consequently, the 5-year survival rates for late-stage gastric tumors are dismally low, and curative treatments for such advanced stages are currently unavailable (Shah & Peek, 2021). The United States is among the few nations that implement routine screening for stomach cancer, emphasizing a preventive approach towards gastrointestinal diseases in these regions (Shah & Peek, 2021).

Helicobacter Pylori Eradication Treatment as Chemoprevention Against Gastric Cancers

Helicobacter pylori (H. pylori) infection is now recognized as a significant pathogenic factor in the development of stomach cancer, which has recently been classified as a class I carcinogen. This bacterium, believed to infect more than half of the global population, instigates predictable disease progression in a small subset (approximately 2%) of those affected. This progression can be halted if detected early. The presence of Cag pathogenicity islands represents a pivotal mechanism through which H. pylori infection may potentially result in cancer development. In addition, there is evidence that suggests that the eradication of H. pylori in individuals with gastric ulcers may reduce the risk of subsequent gastric cancers (Sexton et al., 2020; Shah & Peek, 2021). However, the magnitude of this protective effect varies by geographic region. In regions with high incidence of the disease, such as East Asia, the benefits are more pronounced due to the higher baseline risk. Conversely, in populations with lower risk, such as those in Western regions, the impact of eradication may be comparatively modest.

In this context, Lee et al. conducted a comprehensive meta-analysis, incorporating 22 published studies with data on 715 incident cases of stomach cancer among 48,064 individuals over 340,255 person-years. The objective of the present study was to assess the impact of H. pylori eradication on gastric

cancer outcomes, and how this benefit may vary based on baseline gastric tumor incidence and study methodology (randomized trials versus observational studies). The findings indicated that individuals who underwent H. pylori eradication therapy exhibited a significantly reduced risk of developing gastric cancer, with a pooled incidence rate ratio of 0.53 (95% confidence interval: 0.44-0.64), compared to those who did not receive such treatment.

Aspirin and Non-Steroidal Anti-Inflammatory Drugs as Chemoprevention Agents

The chemopreventive potential of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is particularly notable in the context of adenocarcinomas, a subject that has garnered considerable research interest in malignant prevention. A substantial body of research has identified a correlation between the utilization of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and a notable decrease in the likelihood of developing cancer. This association has been observed to result in a reduction of up to 63% in the risk of developing colorectal cancer and an approximate 40% decrease in the risk of developing breast, lung, and prostate malignancies. However, the molecular mechanisms underlying these chemopreventive effects remain incompletely understood. The efficacy of aspirin and NSAIDs in tumor prevention is likely influenced by various factors, including the site of the tumor, the specific cancer phenotype, and individual variables such as the genetic makeup of the host and environmental factors (Shah & Peek, 2021; W. H. Wang et al., 2003).

α-Difluoromethylornithine as Chemoprevention Against Gastric Malignancies

Treatment with α-difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase, has demonstrated efficacy in directly diminishing the virulence of H. pylori and reducing the risk of gastric dysplasia and carcinoma, as evidenced in studies involving Mongolian gerbils (Sierra et al., 2019). The mechanism by which DFMO exerts its effect involves the reduction of polyamine levels in gastric tissue, thereby counteracting the oxidative stress induced by polyamines. Experimental studies have further revealed that DFMO exerts direct effects on genome stability in H. pylori-infected gastric mucosa. This includes enhancing DNA repair mechanisms and reducing the prevalence of apoptosis-resistant cells with DNA damage. The present study investigates the potential of DFMO as a chemopreventive agent against H. pylori-associated gastric carcinogenesis, as evaluated through ongoing human clinical trials. Furthermore, DFMO, particularly when utilized in conjunction with sulindac, has been observed to exert a chemopreventive effect on the recurrence of colorectal adenomas, likely attributable to its mechanism of polyamine inhibition (Shah & Peek, 2021; Sierra et al., 2019).

Natural Honey as a Chemoprevention of Gastric Cancers

A substantial body of research has underscored the effectiveness of natural honey in both the prevention and treatment of tumors, with a particular focus on stomach cancer. The findings of research conducted on dietary habits suggest that the habitual ingestion of honey may serve as a preventative measure against the development of stomach tumors. Furthermore, honey has been observed to induce apoptosis in gastric mucosal cells, suggesting a potential therapeutic role in the management of gastric malignancies. This apoptotic effect may be attributable to the presence of bioactive compounds in honey, which warrant further investigation to elucidate their precise mechanisms of action in cancer prevention and treatment (Abdel-Latif, 2015).

Chemopreventive Effect of Resveratrol Against Gastric Cancers

Recent findings indicate that resveratrol, recognized for its bactericidal properties, also exhibits the capacity to impede cell proliferation in various human adenocarcinoma cell lines. However, the precise mechanisms underlying these effects remain to be fully elucidated. A pivotal mechanism of resveratrol's inhibitory action in gastric carcinomas (GCs) appears to be the induction of apoptosis through multiple pathways. Research has demonstrated that resveratrol's apoptotic effect is a direct consequence of its capacity to impede cell division (Zulueta et al., 2015).

Conclusion

Chemoprevention is a promising strategy for mitigating the health risks associated with cancer. The notion of leveraging chemoprevention to curtail cancer incidence and mortality rates has garnered support, attributable to the substantiated efficacy of this strategy in diminishing cancer-related fatalities. The development of effective chemopreventive strategies is contingent upon the identification of key risk factors, including genetic predispositions and exposure to environmental carcinogens. The broader acceptance and implementation of chemoprevention are contingent upon the discovery and development of novel agents that are both safe and effective. Advancements in this field necessitate ongoing research and clinical trials to establish a robust arsenal of chemopreventive tools.

Declarations

Funding: The authors declare that there was no funding for this work.

Conflicts of interest/competing interests: The authors have declared no conflicts of interest for this article.

Availability of data and material: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval: not applicable

Consent to participate: Not applicable

Consent for publication: All authors are aware of the submission and have given their consent for publication.

References

Abdel-Hamid, N. M., Abass, S. A., Mohamed, A. A., & Muneam Hamid, D. (2018). Herbal management of hepatocellular carcinoma through cutting the pathways of the common risk factors. *Biomedicine & Pharmacotherapy*, *107*, 1246–1258. https://doi.org/10.1016/j.biopha.2018.08.104

Abdel-Latif, M. M. (2015). Chemoprevention of gastrointestinal cancers by natural honey. *World Journal of Pharmacology*, *4*(1), 160. https://doi.org/10.5497/wjp.v4.i1.160

Abdelmalak, J., Tan, N., Con, D., Eslick, G., Majeed, A., Kemp, W., & Roberts, S. K. (2023). The Effect of Aspirin Use on Incident Hepatocellular Carcinoma—An Updated Systematic Review and Meta-Analysis. *Cancers*, *15*(13), 3518. https://doi.org/10.3390/cancers15133518

Applegate, C., Rowles, J., Ranard, K., Jeon, S., & Erdman, J. (2018). Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients*, *10*(1), 40. https://doi.org/10.3390/nu10010040

Baur, J. A., & Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. *Nature Reviews Drug Discovery*, *5*(6), 493–506. https://doi.org/10.1038/nrd2060

Bonney, A., Malouf, R., Marchal, C., Manners, D., Fong, K. M., Marshall, H. M., Irving, L. B., & Manser, R. (2022). Impact of low-dose computed tomography (LDCT) screening on lung cancer-related mortality. *Cochrane Database of Systematic Reviews*, *2022*(8). https://doi.org/10.1002/14651858.CD013829.pub2

Bonovas, S., Filioussi, K., & Sitaras, N. M. (2005). Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *British Journal of Clinical Pharmacology*, *60*(2), 194–203. https://doi.org/10.1111/j.1365-2125.2005.02386.x

Bujanda, L., Hijona, E., Larzabal, M., Beraza, M., Aldazabal, P., García-Urkia, N., Sarasqueta, C., Cosme, A., Irastorza, B., González, A., & Arenas, J. I. (2008). Resveratrol inhibits nonalcoholic fatty liver disease in rats. *BMC Gastroenterology*, *8*(1), 40. https://doi.org/10.1186/1471-230X-8-40

Choi, J., & Roberts, L. R. (2016). Statins and metformin for chemoprevention of hepatocellular carcinoma. *Clinical Liver Disease*, *8*(2), 48–52. https://doi.org/10.1002/cld.568

Cortés-Jofré, M., Rueda, J.-R., Asenjo-Lobos, C., Madrid, E., & Bonfill Cosp, X. (2020). Drugs for preventing lung cancer in healthy people. *Cochrane Database of Systematic Reviews*, *2020*(3). https://doi.org/10.1002/14651858.CD002141.pub3

Craig, E. L., Stopsack, K. H., Evergren, E., Penn, L. Z., Freedland, S. J., Hamilton, R. J., & Allott, E. H. (2022). Statins and prostate cancer—hype or hope? The epidemiological perspective. *Prostate Cancer and Prostatic Diseases*, *25*(4), 641–649. https://doi.org/10.1038/s41391-022-00554-1

Cruz-Pierard, S. M., Nestares, T., & Amaro-Gahete, F. J. (2022). Vitamin D and Calcium as Key Potential Factors Related to Colorectal Cancer Prevention and Treatment: A Systematic Review. *Nutrients*, *14*(22), 4934. https://doi.org/10.3390/nu14224934

Cui, J.-W., Li, W., Han, F.-J., & Liu, Y.-D. (2015). Screening for lung cancer using low-dose computed tomography: concerns about the application in low-risk individuals. *Translational Lung Cancer Research*, *4*(3), 275–286. https://doi.org/10.3978/j.issn.2218-6751.2015.02.05

Cunha, V., Cotrim, H. P., Rocha, R., Carvalho, K., & Lins-Kusterer, L. (2020). Metformin in the prevention of hepatocellular carcinoma in diabetic patients: A systematic review. *Annals of Hepatology*, *19*(3), 232–237. https://doi.org/10.1016/j.aohep.2019.10.005

Cuzick, J., Sestak, I., Cawthorn, S., Hamed, H., Holli, K., Howell, A., & Forbes, J. F. (2015). Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *The Lancet Oncology*, *16*(1), 67–75. https://doi.org/10.1016/S1470-2045(14)71171-4

Daugherty, S. E., Pfeiffer, R. M., Sigurdson, A. J., Hayes, R. B., Leitzmann, M., Schatzkin, A., Hollenbeck, A. R., & Silverman, D. T. (2011). Nonsteroidal Antiinflammatory Drugs and Bladder Cancer: A Pooled Analysis. *American Journal of Epidemiology*, *173*(7), 721–730. https://doi.org/10.1093/aje/kwq437

Dobruch, J., & Oszczudłowski, M. (2021). Bladder Cancer: Current Challenges and Future Directions. *Medicina*, *57*(8), 749. https://doi.org/10.3390/medicina57080749

G., M. S., Swetha, M., Keerthana, C. K., Rayginia, T. P., & Anto, R. J. (2022). Cancer Chemoprevention: A Strategic Approach Using Phytochemicals. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.809308

Goh, M. J., & Sinn, D. H. (2022). Statin and aspirin for chemoprevention of hepatocellular carcinoma: Time to use or wait further? *Clinical and Molecular Hepatology*, *28*(3), 380–395. https://doi.org/10.3350/cmh.2021.0366

Gold, K. A., Kim, E. S., Wistuba, I. I., & Hong, W. K. (2012). *Personalizing Lung Cancer Prevention Through a Reverse Migration Strategy* (pp. 221–240). https://doi.org/10.1007/128_2012_338

Gupta, P., Wright, S. E., Kim, S.-H., & Srivastava, S. K. (2014). Phenethyl isothiocyanate: A comprehensive review of anti-cancer mechanisms. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, *1846*(2), 405–424. https://doi.org/10.1016/j.bbcan.2014.08.003

Hunsu, V. O., Facey, C. O. B., Fields, J. Z., & Boman, B. M. (2021). Retinoids as Chemo-Preventive and Molecular-Targeted Anti-Cancer Therapies. *International Journal of Molecular Sciences*, *22*(14), 7731. https://doi.org/10.3390/ijms22147731

Jackson, S. E., & Chester, J. D. (2015). Personalised cancer medicine. *International Journal of Cancer*, *137*(2), 262–266. https://doi.org/10.1002/ijc.28940

Jiminez, V., & Yusuf, N. (2023). An update on clinical trials for chemoprevention of human skin cancer. *Journal of Cancer Metastasis and Treatment*, *9*(1). https://doi.org/10.20517/2394-4722.2022.99

Kathawala, R. J., Kudelka, A., & Rigas, B. (2018). The Chemoprevention of Ovarian Cancer: the Need and the Options. *Current Pharmacology Reports*, *4*(3), 250–260. https://doi.org/10.1007/s40495-018-0133-6

Keith, R. L., Blatchford, P. J., Merrick, D. T., Bunn, P. A., Bagwell, B., Dwyer-Nield, L. D., Jackson, M. K., Geraci, M. W., & Miller, Y. E. (2019). A Randomized Phase II Trial of Pioglitazone for Lung Cancer Chemoprevention in High-Risk Current and Former Smokers. *Cancer Prevention Research*, *12*(10), 721–730. https://doi.org/10.1158/1940-6207.CAPR-19-0006

Ledesma, M. C., Jung-Hynes, B., Schmit, T. L., Kumar, R., Mukhtar, H., & Ahmad, N. (2011). Selenium and Vitamin E for Prostate Cancer: Post-SELECT (Selenium and Vitamin E Cancer Prevention Trial) Status. *Molecular Medicine*, *17*(1–2), 134–143. https://doi.org/10.2119/molmed.2010.00136

Lee, J. Y., Sim, T.-B., Lee, J., & Na, H.-K. (2017). Chemopreventive and Chemotherapeutic Effects of Fish Oil derived Omega-3 Polyunsaturated Fatty Acids on Colon Carcinogenesis. *Clinical Nutrition Research*, *6*(3), 147. https://doi.org/10.7762/cnr.2017.6.3.147

Leone, A., Diorio, G., Sexton, W., Schell, M., Alexandrow, M., Fahey, J. W., & Kumar, N. B. (2017). Sulforaphane for the chemoprevention of bladder cancer: molecular mechanism targeted approach. *Oncotarget*, *8*(21), 35412–35424. https://doi.org/10.18632/oncotarget.16015

Liu, C.-Q., Sun, J.-X., Xu, J.-Z., Qian, X.-Y., Hong, S.-Y., Xu, M.-Y., An, Y., Xia, Q.-D., Hu, J., & Wang, S.-G. (2022). Metformin Use on Incidence and Oncologic Outcomes of Bladder Cancer Patients With T2DM: An Updated Meta-Analysis. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.865988

Liu, D., & Chen, Z. (2013). The Effect of Curcumin on Breast Cancer Cells. *Journal of Breast Cancer*, *16*(2), 133. https://doi.org/10.4048/jbc.2013.16.2.133

Lung Cancer Prevention (PDQ®) - NCI - –Health Professional Version. (2025). National Cancer Institute. https://www.cancer.gov/types/lung/hp/lung-prevention-pdq

Maniewska, J., & Jeżewska, D. (2021). Non-Steroidal Anti-Inflammatory Drugs in Colorectal Cancer Chemoprevention. *Cancers*, *13*(4), 594. https://doi.org/10.3390/cancers13040594

Mao, J. T., Lu, Q.-Y., Xue, B., Neis, P., Zamora, F. D., Lundmark, L., Qualls, C., & Massie, L. (2019). A Pilot Study of a Grape Seed Procyanidin Extract for Lung Cancer Chemoprevention. *Cancer Prevention Research*, *12*(8), 557–566. https://doi.org/10.1158/1940-6207.CAPR-19-0053

Marchesini, G., Bianchi, G., Tomassetti, S., Zoli, M., & Melchionda, N. (2001). Metformin in non-alcoholic steatohepatitis. *The Lancet*, *358*(9285), 893–894. https://doi.org/10.1016/S0140-6736(01)06042-1

Minokawa, Y., Sawada, Y., & Nakamura, M. (2021). The Influences of Omega-3 Polyunsaturated Fatty Acids on the Development of Skin Cancers. *Diagnostics*, *11*(11), 2149. https://doi.org/10.3390/diagnostics11112149

MOKBEL, K., WAZIR, U., & MOKBEL, K. (2019). Chemoprevention of Prostate Cancer by Natural Agents: Evidence from Molecular and Epidemiological Studies. *Anticancer Research*, *39*(10), 5231–5259. https://doi.org/10.21873/anticanres.13720

Pashayan, N., Antoniou, A. C., Ivanus, U., Esserman, L. J., Easton, D. F., French, D., Sroczynski, G., Hall, P., Cuzick, J., Evans, D. G., Simard, J., Garcia-Closas, M., Schmutzler, R., Wegwarth, O., Pharoah, P., Moorthie, S., De Montgolfier, S., Baron, C., Herceg, Z.,

… Widschwendter, M. (2020). Personalized early detection and prevention of breast cancer: ENVISION consensus statement. *Nature Reviews Clinical Oncology*, *17*(11), 687–705. https://doi.org/10.1038/s41571-020-0388-9

Ramchatesingh, B., Martínez Villarreal, A., Arcuri, D., Lagacé, F., Setah, S. A., Touma, F., Al-Badarin, F., & Litvinov, I. V. (2022). The Use of Retinoids for the Prevention and Treatment of Skin Cancers: An Updated Review. *International Journal of Molecular Sciences*, *23*(20), 12622. https://doi.org/10.3390/ijms232012622

Ranjan, A., Ramachandran, S., Gupta, N., Kaushik, I., Wright, S., Srivastava, S., Das, H., Srivastava, S., Prasad, S., & Srivastava, S. K. (2019). Role of Phytochemicals in Cancer Prevention. *International Journal of Molecular Sciences*, *20*(20), 4981. https://doi.org/10.3390/ijms20204981

Rivero, J. R., Thompson, I. M., Liss, M. A., & Kaushik, D. (2018). Chemoprevention in Prostate Cancer: Current Perspective and Future Directions. *Cold Spring Harbor Perspectives in Medicine*, *8*(10), a030494. https://doi.org/10.1101/cshperspect.a030494

Russo, M., Spagnuolo, C., Tedesco, I., & Russo, G. L. (2010). Phytochemicals in Cancer Prevention and Therapy: Truth or Dare? *Toxins*, *2*(4), 517–551. https://doi.org/10.3390/toxins2040517

Sahin, K., Orhan, C., Tuzcu, M., Sahin, N., Tastan, H., Özercan, İ. H., Güler, O., Kahraman, N., Kucuk, O., & Ozpolat, B. (2018). Chemopreventive and Antitumor Efficacy of Curcumin in a Spontaneously Developing Hen Ovarian Cancer Model. *Cancer Prevention Research*, *11*(1), 59–67. https://doi.org/10.1158/1940-6207.CAPR-16-0289

Sawicki, T., Ruszkowska, M., Danielewicz, A., Niedźwiedzka, E., Arłukowicz, T., & Przybyłowicz, K. E. (2021). A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis. *Cancers*, *13*(9), 2025. https://doi.org/10.3390/cancers13092025

Schrijver, L. H., Antoniou, A. C., Olsson, H., Mooij, T. M., Roos-Blom, M.-J., Azarang, L., Adlard, J., Ahmed, M., Barrowdale, D., Davidson, R., Donaldson, A., Eeles, R., Evans, D. G., Frost, D., Henderson, A., Izatt, L., Ong, K.-R., Bonadona, V., Coupier, I., … van den Broek, E. C. (2021). Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study. *American Journal of Obstetrics and Gynecology*, *225*(1), 51.e1-51.e17. https://doi.org/10.1016/j.ajog.2021.01.014

Sexton, R. E., Al Hallak, M. N., Diab, M., & Azmi, A. S. (2020). Gastric cancer: a comprehensive review of current and future treatment strategies. *Cancer and Metastasis Reviews*, *39*(4), 1179–1203. https://doi.org/10.1007/s10555-020-09925-3

Shah, S. C., & Peek, R. M. (2021). Chemoprevention Against Gastric Cancer. *Gastrointestinal Endoscopy Clinics of North America*, *31*(3), 519–542. https://doi.org/10.1016/j.giec.2021.03.006

SHANG, J., CHEN, L., XIAO, F., SUN, H., DING, H., & XIAO, H. (2008). Resveratrol improves non-alcoholic fatty liver disease by activating AMP-activated protein kinase. *Acta Pharmacologica Sinica*, *29*(6), 698–706. https://doi.org/10.1111/j.1745-7254.2008.00807.x

Shang, Z., Wang, X., Yan, H., Cui, B., Wang, Q., Wu, J., Cui, X., Li, J., Ou, T., & Yang, K. (2018). Intake of Non-steroidal Anti-inflammatory Drugs and the Risk of Prostate Cancer: A Meta-Analysis. *Frontiers in Oncology*, *8*. https://doi.org/10.3389/fonc.2018.00437

Sierra, J. C., Suarez, G., Piazuelo, M. B., Luis, P. B., Baker, D. R., Romero-Gallo, J., Barry, D. P., Schneider, C., Morgan, D. R., Peek, R. M., Gobert, A. P., & Wilson, K. T. (2019). α-Difluoromethylornithine reduces gastric carcinogenesis by causing mutations in *Helicobacter pylori cagY*. *Proceedings of the National Academy of Sciences*, *116*(11), 5077–5085. https://doi.org/10.1073/pnas.1814497116

Singh, A. K., Singh, S. V., Kumar, R., Kumar, S., Senapati, S., & Pandey, A. K. (2023). Current therapeutic modalities and chemopreventive role of natural products in liver cancer: Progress and promise. *World Journal of Hepatology*, *15*(1), 1–18. https://doi.org/10.4254/wjh.v15.i1.1

Singh, M., Suman, S., & Shukla, Y. (2014). New Enlightenment of Skin Cancer Chemoprevention through Phytochemicals: *In Vitro* and *In Vivo* Studies and the Underlying Mechanisms. *BioMed Research International*, *2014*, 1–18. https://doi.org/10.1155/2014/243452

Song, X., Zhang, M., Dai, E., & Luo, Y. (2018). Molecular targets of curcumin in breast cancer (Review). *Molecular Medicine Reports*. https://doi.org/10.3892/mmr.2018.9665

Tow, R., Hanoun, S., Andresen, B., Shahid, A., Wang, J., Kelly, K. M., Meyskens, F. L., & Huang, Y. (2023). Recent Advances in Clinical Research for Skin Cancer Chemoprevention. *Cancers*, *15*(15), 3819. https://doi.org/10.3390/cancers15153819

Trabert, B., Poole, E. M., White, E., Visvanathan, K., Adami, H.-O., Anderson, G. L., Brasky, T. M., Brinton, L. A., Fortner, R. T., Gaudet, M., Hartge, P., Hoffman-Bolton, J., Jones, M., Lacey, J. V, Larsson, S. C., Mackenzie, G. G., Schouten, L. J., Sandler, D. P.,

O'Brien, K., … Tworoger, S. S. (2019). Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium. *JNCI: Journal of the National Cancer Institute*, *111*(2), 137–145. https://doi.org/10.1093/jnci/djy100

Tratnjek, L., Jeruc, J., Romih, R., & Zupančič, D. (2021). Vitamin A and Retinoids in Bladder Cancer Chemoprevention and Treatment: A Narrative Review of Current Evidence, Challenges and Future Prospects. *International Journal of Molecular Sciences*, *22*(7), 3510. https://doi.org/10.3390/ijms22073510

Umezawa, S., Higurashi, T., Komiya, Y., Arimoto, J., Horita, N., Kaneko, T., Iwasaki, M., Nakagama, H., & Nakajima, A. (2019). Chemoprevention of colorectal cancer: Past, present, and future. *Cancer Science*, *110*(10), 3018–3026. https://doi.org/10.1111/cas.14149

Wang, G.-L., Fu, Y.-C., Xu, W.-C., Feng, Y.-Q., Fang, S.-R., & Zhou, X.-H. (2009). Resveratrol inhibits the expression of SREBP1 in cell model of steatosis via Sirt1–FOXO1 signaling pathway. *Biochemical and Biophysical Research Communications*, *380*(3), 644–649. https://doi.org/10.1016/j.bbrc.2009.01.163

Wang, W. H., Huang, J. Q., Zheng, G. F., Lam, S. K., Karlberg, J., & Wong, B. C.-Y. (2003). Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *Journal of the National Cancer Institute*, *95*(23), 1784–1791. https://doi.org/10.1093/jnci/djg106

Whitsett Jr, T. G., & Lamartiniere, C. A. (2006). Genistein and resveratrol: mammary cancer chemoprevention and mechanisms of action in the rat. *Expert Review of Anticancer Therapy*, *6*(12), 1699–1706. https://doi.org/10.1586/14737140.6.12.1699

Xiao, Q., Xiao, J., Liu, J., Liu, J., Shu, G., & Yin, G. (2022). Metformin suppresses the growth of colorectal cancer by targeting INHBA to inhibit TGF-β/PI3K/AKT signaling transduction. *Cell Death & Disease*, *13*(3), 202. https://doi.org/10.1038/s41419-022-04649-4

Xin, P., Han, H., Gao, D., Cui, W., Yang, X., Ying, C., Sun, X., & Hao, L. (2013). Alleviative effects of resveratrol on nonalcoholic fatty liver disease are associated with up regulation of hepatic low density lipoprotein receptor and scavenger receptor class B type I gene expressions in rats. *Food and Chemical Toxicology*, *52*, 12–18. https://doi.org/10.1016/j.fct.2012.10.026

Yang, F.-R., Li, S.-Y., Hu, X.-W., Li, X.-R., & Li, H.-J. (2022). Identifying the Antitumor Effects of Curcumin on Lung Adenocarcinoma Using Comprehensive Bioinformatics Analysis. *Drug Design, Development and Therapy*, *Volume 16*, 2365–2382. https://doi.org/10.2147/DDDT.S371420

Zhang, J., Lei, Z., Huang, Z., Zhang, X., Zhou, Y., Luo, Z., Zeng, W., Su, J., Peng, C., & Chen, X. (2016). Epigallocatechin-3-gallate(EGCG) suppresses melanoma cell growth and metastasis by targeting TRAF6 activity. *Oncotarget*, *7*(48), 79557–79571. https://doi.org/10.18632/oncotarget.12836

Zulueta, A., Caretti, A., Signorelli, P., & Ghidoni, R. (2015). Resveratrol: A potential challenger against gastric cancer. *World Journal of Gastroenterology*, *21*(37), 10636–10643. https://doi.org/10.3748/wjg.v21.i37.10636.