A Review Based on How Smoking May Contribute to Urinary Adenocarcinoma Also How Garlic Helps to Prevent It

Submitted by,

Name: Md. Mehrab F Rahman

ID: 19346060

A thesis submitted to the School of Pharmacy to fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

Brac University

March 2025

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Md. Mehrab F Rahman
19346060

Approval

The thesis titled is “A review based on how smoking may contribute to bladder cancer also how garlic can prevent bladder cancer” submitted by Md. Mehrab F Rahman (19346060), of Summer, 2024 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Dr. Mohd Raeed Jamiruddin
Associate Professor
School of Pharmacy
BRAC University

Approved By:

Dean:

A.F.M. Yusuf Haider, PhD
Acting Dean, School of Pharmacy
Professor, Department of Mathematics and Natural Science
BRAC University

Dedication

I dedicated to my faculty members, family and friends.

Ethics Statement

There were no human participants, human specimens or tissue or animals or field research in this study.

Abstract

Urinary adenocarcinoma which is a form of bladder cancer remains to be a major global health issue where smoking recognized as a prominent risk factor. Carcinogenic components in cigarette smoke, such as nitrosamines, polycyclic aromatic hydrocarbons, and reactive oxygen species, promote this type of cancer by such processes including DNA damage, oxidative stress, and chronic inflammation. These mechanisms activate major carcinogenic pathways, such as NF-κB and COX-2/PGE2 which promotes tumor progression. On the other hand, garlic (Allium sativum) shows anticancer effects, primarily due to its bioactive compounds like allicin, DADS, and DATS. These chemicals reduce oxidative stress, inflammatory pathways, and promote apoptosis in cancer cells. Garlic shows effect on signaling pathways, such as NF-κB, PI3K/AKT, and MAPK which lower down the tumor promoting effect caused by smoking. This review highlights the molecular mechanisms associated with smoking-induced bladder cancer and the protective role of garlic. Also, it proposes garlic's potential as a dietary intervention for cancer prevention.

Keywords: Smoking, Bladder Cancer, Molecular Mechanisms, Oxidative Stress, Inflammation, Garlic, Anticancer Properties

Acknowledgement

It was a great experience for me to work with so many wonderful people of school of pharmacy. I am thanks to almighty Allah to give me this opportunity and also making my journey more idealistic and encouraging.

Firstly, I admire my supervisor, Mohd. Raeed Jamiruddin, PhD, an Associate professor at Brac University's School of Pharmacy, for allowing me to work as one of his thesis students. His assistance, direction, commitment, passion, and knowledge in this field have also increased my interest in thesis work and encourage me to finish the research correctly.

Secondly, I would like to thank all the faculty member who have imparted their knowledge to me. It makes my bachelor journey easy and convenient. Also, I would like to thanks the A.F.M. Yusuf Haider, PhD (Acting Dean of the school of Pharmacy) for his constant support.

Finally, I would like to express my full gratitude to all of the senior, friends and family member for supporting me all the time.

Table of Contents

List of Tables

List of Figures

List of Acronyms

COX-2 – Cyclooxygenase-2

PAHs – Polycyclic Aromatic Hydrocarbons

PGE2 – Prostaglandin E2

ROS – Reactive Oxygen Species

TP53 – Tumor Protein 53

VEGF – Vascular Endothelial Growth Factor

DADS – Diallyl Disulfide

MDA – Malondialdehyde

TxA2 – Thromboxane A2

ERK – Extracellular Signal-Regulated Kinase

PI3K/AKT – Phosphoinositide 3-Kinase

TNF-α – Tumor Necrosis Factor-alpha

Chapter 1

Introduction

1.1 Overview

Urinary adenocarcinoma is an uncommon form of cancer that arises from glandular cells in the urinary tract. These glandular cells are typically found in the lining of the bladder, urethra, or other parts of the urinary system. Unlike the more common transitional cell carcinoma, adenocarcinoma involves cells that have glandular characteristics (Popov et al., 2023). Although this kind of cancer can develop anywhere throughout the urinary tract, it usually appears in the bladder. It can also occur in the urethra and other parts of the urinary system.

Urinary adenocarcinoma presents frequently with various symptoms that can substantially affect a patient's quality of life. The most common symptom is hematuria, or blood in the urine, which can be visible to the naked eye or detected microscopically. Patients may also experience dysuria, characterized by irritation or a burning feeling during urination. Increased urinary frequency and frequency are common complaints, with patients feeling a persistent need to urinate even when the bladder is not full. Additionally, some individuals may report pelvic pain or discomfort, which can be dull or sharp and may worsen over time (Roy & Parwani, 2011). In advanced cases, symptoms may include weight loss, fatigue, and general malaise. Individuals showing these symptoms need to seek medical evaluation, since immediate finding and intervention might enhance results. and reduce complications associated with urinary adenocarcinoma.

Smoking causes urinary adenocarcinoma through the chronic exposure to carcinogens, mainly nitrosamines (NNK) and polycyclic aromatic hydrocarbons (PAHs), which are excreted through urine and accumulate in the bladder. These carcinogens cause direct DNA damage for that it causes

uncontrolled cell growth. Additionally, smoking triggers oxidative stress and chronic inflammation, activating pathways like NF-κB and COX-2/PGE2.

On the other hand, Ginger is another herb that can be used to treat bladder cancer. Gingerol and paradol, two of the many elements of ginger, have shown anticancer activity against various tumoral cell lines in vitro (Wigner et al., 2021). Bioactive compounds like 6-gingerol, and paradols neutralize oxidative stress by removing free radicals. by this away it prevents further DNA damage and mutations. Ginger also inhibits chronic inflammation by reducing NF-κB and COX-2/PGE2 signaling, which reduces tumor-promoting inflammation and angiogenesis. By this way ginger helps slow tumor progression, enhances cancer cell death, and helps in the recovery from smoking-induced urinary adenocarcinoma.

1.2 Background: Prevalence, Risk Factor and Cure

Urinary adenocarcinoma is among the most popular cancers in the world. There are roughly 550,000 new cases of bladder cancer diagnosed each year, making it top 10 most frequent malignancies. It is mostly common on the developed communities (Richters, et al., 2020). Rates of incidence differ significantly across different geographic regions. Europe, the United States of America, and Egypt have the greatest rates. On the other hand, sub-Saharan Africa, Asia, and South America display the lowest percentages (Goodman, M., & Jemal, A, 2014). Research examining data from Sri Lanka indicated a rate of 1.36 per 100,000 in males and 0.3 per 100,000 in females. These rates are similar to other South Asian countries like Bangladesh and others but lower than UK and USA (Ranasinghe, et al., 2012).

Adenocarcinomas arise from glandular cells, which are not normally present in the bladder lining, but may appear due to chronic irritation, inflammation, or congenital abnormalities (Popov et al., 2023). It has been determined that smoking is one of the main causes of bladder cancer development (Anderson, n.d.) According to Paul L Skipper (2003), The risk of bladder cancer is approximately three times higher for existing smokers than for non-smokers, and it is twice as high for ex-smokers. The main way that smoking cigarettes causes bladder cancer is through exposure to the aromatic amines in tobacco smoke (2-naphthylamine and 4-aminobiphenyl) (Office of the Surgeon General, 2010). It has also been proven that smoking and cigarette smoke exposure during childhood raise the probability of bladder cancer (Anderson, n.d.). Also, the risk increased depending on the duration of the smoking. Study shows that there was a direct connection between longer smoking duration and an increased risk of bladder cancer, with the risk increasing by about two times for less than ten years and more than four times for more than forty years. Up to a threshold limit of 15–20 cigarettes per day (Brennan et al., n.d.).

In order to lower the rate of smoking-related illnesses, such as urinary adenocarcinoma, smoking prevention is essential. Public education initiatives, tobacco prices, advertising limits, and smoking prohibitions in public places are all examples of steps to lower down the rate of smoking (Jha & Peto, 2014). By this way, disease like adenocarcinoma which is potentially caused by smoking, ginger anti-inflammatory and anti-oxidant effect reduce it (Habib et al., 2008).

1.3 Rationale

The rationale of the project is to identify the relation between smoking and urinary adenocarcinoma and to explore garlic’s potential role in the prevention of cancer. Smoking is the primary cause of urinary adenocarcinoma due to its carcinogenic compound. The aim of this study is to provide background information for further research into the mechanism through which smoking causes urinary adenocarcinoma and how garlic reduce those effect.

Garlic is commonly known for its anti carcer properties. it has active compound can modulate pathway which involved in the cancer development. Studying garlic's ability to reduce cellular damage caused by smoking may show its importance in preventing bladder cancer. The aim of this thesis to provide a foundation to reduce the impact of smoking on urinary adenocarcinoma.

1.4 Objective

The objective of this thesis is to gather and calculate some existing information of role of smoking and how it causes urinary adenocarcinoma and also determine the potential role of garlic in the prevention of Urinary Adenocarcinoma. This thesis mainly focuses on the molecular mechanism by which smoking include carcinogens in the urinary tract. It will also focus on the signaling pathway. Additionally, it will also examine how garlic inhibit this process. By examining all these mechanisms, this review will give us an overview of carcinogenic pathway which is caused by smoking and anticancer potential of garlic for supporting further studies for urinary cancer prevention.

Chapter 2
Methodology

This review examines the influence of smoking on urinary adenocarcinoma and the possible preventative effects of garlic. Data for this study were compiled from research articles sourced from reputable databases, including PubMed, Elsevier, ScienceDirect, Springer, Nature, and Google Scholar. The searches were conducted using a combination of keywords that align with the research topic. Research examining the molecular mechanisms and signaling pathways associated with smoking-induced carcinogenesis in the urinary tract, with investigations into the anti-cancer properties of garlic components.

2.1 Number of results

The search result shows approximately 444 research articles across different websites. The contribution of each website is given below;

Table 1: Keywords search result

	keyword	Result
PubMed	(smoking) AND (urinary adenocarcinoma)	18
	((cancer) AND (smoking)) AND (cox-2)	21
	((smoking) AND (oxidative stress)) AND (DNA damage)	90
	((molecular mechanism) AND (smoking)) AND (carcinogenic)	37
	((NF-κB) AND (inflammation)) AND (bladder cancer)	6

	(((molecular mechanism) AND (ROS)) AND (bladder cancer)) AND (smoking)	1
	(garlic) AND (anti-cancer)	10
	((garlic) AND (cancer)) AND (molecular mechanism)	13
	(((Signaling Pathway) AND (garlic)) AND (NF-κB)) AND (Suppress Tumor)	3
	(((MAPK Signaling) AND (anti-cancer)) AND (garlic)) AND (Apoptosis)	1
	((DADS) AND (cell cycle)) AND (DNA damage)	2
Google Scholar	((smoking) AND (adenocarcinoma)) AND (DNA damage)	1
	(((smoking) AND (adenocarcinoma)) AND (cox-2)) AND (signaling pathway)	2
	((garlic) AND (anti-cancer)) AND (compound)	4
Nature	(((molecular mechanism) AND (ROS)) AND (bladder cancer)) AND (smoking)	210
	(((Signaling Pathway) AND (garlic)) AND (NF-κB)) AND (Suppress Tumor)	17
	((((DADS) AND (cell cycle)))) AND (DNA damage))) AND (cancer)) AND (smoking)	3
	((((MAPK Signaling) AND (anti-cancer))) AND (garlic)) AND (Apoptosis)) AND (NF-κB)	5

2.2 Inclusion Criteria

To ensure the authenticity and the reliability of the information, the following inclusion criteria were applied:

Journals that are only peer-reviewed are mostly selected. Article are also chosen based on their published date. To get the current information this research focused on the article that published within last 25 years. Research also focused on the molecular pathway linking smoking with urinary adenocarcinoma. Also, the bioactive compounds in garlic and their potential anticancer properties.

2.3 Exclusion Criteria

Article are excluded which are lack of molecular mechanism of garlic and smoking induced cancer. Article which are not in English are avoided. Also, Articles discussing general cancer risk factors without specific relevance to smoking or garlic.

2.4 Data Extraction and Analysis

After applying the inclusion and exclusion criteria, almost 50 research papers were selected for the review. The selected studies were analyzed based on smoking and its role in urinary adenocarcinoma, molecular pathways and potential mechanisms by which garlic may counteract smoking-induced oxidative stress and inflammation.

The information was carefully evaluated, summarized, and appropriately referenced to provide readers with an in-depth knowledge of the relationship between smoking and urinary adenocarcinoma, along with the potential role of garlic in cancer prevention.

Chapter 3

Smoking and Bladder Cancer

3.1 Carcinogenic Compounds in Tobacco Smoke

Tobacco smoking is the most well-documented risk factor for bladder cancer in men and women. For long time of developing the component of smoke, its changes a lot. Over the time, the number of the cases remain stable but now it can be seen that during the reduction of composition such as Tar and nicotine, it is developing (Freedman et al., n.d.) However, there has also been a noticeable rise in the concentration of certain carcinogens, such as beta-napthylamine, which is a known bladder carcinogen, and tobacco-specific nitrosamines. (Freedman et al., n.d.). Other than this, some carcinogenic compounds are Aromatic amine, polycyclic aromatic hydrocarbons, reactive oxygen species etc.

Aromatic Amines,

Table 2: Aromatics Amines compound whit the quantity per cigarette

Chemical family	Compound	Quantity per cigarette
Aromatic amines	2-naphthylamine	1–22 ng
	4-aminobiphenyl	2–5 ng
	2-toluidine	30–200 ng
	2,6-dimethylaniline	4–50 ng

Researchers claim that aromatic amines in smoking, include 4-aminobiphenyl, may cause DNA changes in the bladder's glandular cells, which may lead to both urothelial cancer and

adenocarcinoma. Long-term exposure of the urinary cells with metabolites of these amines raises the chance of various kinds of histologic cancer (Al-Zalabani et al., 2016).

Polycyclic Aromatic Hydrocarbons (PAHs)

Table 3: Polycyclic Aromatic Hydrocarbons compound and quantity per cigarette

Chemical family	Compound	Quantity per cigarette
Polycyclic aromatic hydrocarbons	Benzo[a]pyrene	8.5–17.6 ng
	Benz[a]anthracene	20–70 ng
	Dibenz[a,h]anthracene	4 ng
	Benzo[b]fluorathene	4–22 ng
	Benzo[j]fluorathene	6–21 ng
	Benzo[k]fluorathene	6–12 ng
	Dibenzo[a,i]pyrene	1.7–3.2 ng
	Dibenzo[a,e]pyrene	Present
	Indenol[1,2,3-cd]pyrene	4–20 ng
	5-methylchrysene	U-0.6 ng

Polycyclic aromatic hydrocarbons (PAHs) in cigarette smoke, includes benzo[a]pyrene, represent a significant type of carcinogens. These substances create DNA adducts and promote mutations in tumor suppressor genes (e.g., TP53) and oncogenes, which contribute to the development of bladder cancer.

Reactive Oxygen Species (ROS)

Smoke usually produces various ROS. Those contains hydrogen peroxide, superoxide etc. Both urothelial and glandular cells are affected by the production of these ROS. This results in DNA damage and causes carcinogenesis in the urinary tract. Long time exposer to this can lead to cellular and genetic change which eventually cause the development of adenocarcinoma (Cha et al., 2023).

Nitrosamines,

Table 4: Nitrosamines compound and quantity per cigarette (Hecht, n.d.)

Chemical family	Compound	Quantity per cigarette
N-nitrosamines	N-nitrosonornicotine	154–196 ng
	4-(methy1nitrosamino)-1-(3-pyridyl)-1-butanone	110–133 ng
	N-nitrosodimethylamine	0.1–180 ng
	N-nitrosodiethylamine	U-25 ng
	N-nitrosoethylmethylamine	U-13 ng
	N-nitrosopyrrolidine	1.5–110 ng
	N-nitrosopiperidine	U-9 ng
	N-nitrosodiethanolamine	U-9 ng

Nitrosamines such as NDMA are known to produce abnormalities in tumor suppressor genes and oncogenes, which contribute to both urothelial and adenocarcinoma (Hecht, n.d.). Nitrosamines, especially due to their alkylating properties, are linked to DNA damage and have been implicated in several cancers within the urinary system.

3.2 Molecular Mechanisms in Bladder Cancer: Detail mechanisms like DNA damage, oxidative stress, and inflammation

DNA Damage:

Bladder cancer has a significant connection with smoking because it causes major DNA damage. Tobacco smoke comprises several carcinogenic substances, such as polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and reactive oxygen species (ROS), and these directly damage cellular DNA or did damage via secondary metabolites (Cadet, et al., 2003). The DNA damage induced by these substances mainly include the creation of DNA adducts, single-strand breaks (SSBs), and oxidized bases such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) (ESCODD, 2003).

Guanine is the DNA base that is most easily damaged by oxidation because it has the lowest redox potential. Oxidized guanine, like 8-oxodG, can easily be inappropriately pair with adenine when DNA is replicated (Reszka, et al., 2020). By this it causes G:C → T: A transversion mutations—a hallmark of smoking-induced carcinogenesis (Jiang, 2009). These changes often happen in important tumor suppressor genes like TP53 and RB1, which are often inactivated in bladder cancer. When these genes don't work properly, it affects the control of cell division and cell death, leading to the rapid growth of broken cells (Savina, 2016). Carcinogens such as 4-aminobiphenyl and 2-naphthylamine are found in tobacco smoke, which is a primary risk factor. These carcinogens stimulate the production of DNA adducts, which in effect leads to mutations in oncogenes (such as TP53) and hormones that regulate tumor growth. These carcinogens are responsible for the modifications of DNA bases and the breaks in DNA strands that eventually lead to genotoxic effects. (Hogg R. C. 2016).

DNA repair processes like base excision repair (BER) and nucleotide excision repair (NER) usually fix damage caused by oxidation and chemical attachments. But long-term smoking damages these repair systems, causing mistakes in repairs or constant issues which end up in genetic instability (Alsaad, et al.,2019). When DNA damage is not fixed properly, it can cause changes in chromosomes and increase the amount of oncogenes, which can lead to the start and growth of tumors (Chevillard, et al., 1998). Being constantly exposed to DNA damage leads to a specific pattern of mutations in bladder cancer, which is often connected to smoking. This shows a link between smoking and the cause of the disease.

Oxidative stress:

Oxidative stress is a state that involves an imbalance between the formation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, resulting in cellular damage. ROS are very reactive chemicals that have the ability to cause damage to lipids, proteins, and DNA, which can impair cellular functions (Sawicka, et al., 2015). Smoking considerably contributes to oxidative stress due to the high concentration of free radicals and pro-oxidants in cigarette smoke (Islam, 2019)

Reactive oxygen species (ROS) include both free radical and non-free radical oxygen intermediates, such as hydrogen peroxide, superoxide, singlet oxygen, and the hydroxyl radical (Liou, et al., 2010). ROS cause strand breakage, alter DNA bases. Oxidative stress usually damages some molecule like DNA, proteins etc. ROS breaks DNA strands and modify DNA base and generate abasic site. ROS also promote lipid peroxidation (Patchsung, et al., 2012). By this it generates byproducts such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE), which further form DNA and protein adducts. For this reason, it amplifies cellular damage (Gecit, et al., 2017).

Furthermore, oxidative stress activates carcinogenic signaling pathways in along with directly causing damage. For example, ROS stimulate the NF-κB pathway, which promotes inflammation and creates an environment suitable to tumor growth (Banan, et al., 2004). Chronic oxidative stress also results in mitochondrial dysfunction (Cotter, T. G. 2004). The development of bladder cancer is significantly influenced by the continuous oxidative damage that results from saturated antioxidant systems, which causes mutations, epigenetic changes, and cellular transformation.

Inflammation:

Inflammation significantly contributes to smoking-induced bladder cancer by establishing a tumor-promoting environment. Tobacco smoke-induced oxidative stress triggers inflammatory pathways, which lead to the activation of immune cells like neutrophils and macrophages, which then release ROS and inflammatory cytokines (Sui, et al., 2017).

Oxidative stress activates nuclear factor-kappa B (NF-κB), a critical mediator of smoking-induced inflammation. NF-κB regulates the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) (Wigner, et al., 2021). All these cytokines increase tumor growth promoting angiogenesis (development of fresh blood vessels) and preventing apoptosis. In addition, chronic inflammation inhibits immune surveillance, which makes it possible for cancer cells to avoid being destroyed by the immune system (Pang, et al., 2016).

On the other hand, because of smoking-induced oxidative activate another important inflammatory process including cyclooxygenase-2 (COX-2). COX-2 stimulates the production of prostaglandins, which then increase the metastasis and proliferation of cancer cells (Boström, et al., 2001). Matrix metalloproteinases (MMPs) released by inflammatory cells further damage the extracellular matrix, allowing cancer cells to more easily spread and invade (Kömhoff, et al., 2000).

The development of bladder cancer is driven by a self-sustaining environment that is created by a cycle of oxidative stress, inflammation, and DNA damage. Tobacco uses not only starts but also keeps this process going, which makes bladder cancers more aggressive and more likely to come back (Reuter, et al., 2010).

3.3 Signaling Pathways: Smoking induced signals in cancer cells

Cigarette smoke promotes complex signaling pathways that facilitate carcinogenesis, inflammation, and angiogenesis in urinary adenocarcinoma. Smoking significantly affects the COX-2/PGE2 signaling system, which play a curtail role throughout the pro-inflammatory responses. Cigarette smoke enhances the proliferation of the COX-2 gene in urothelial tissues, resulting in increased COX enzymatic activity and excessive pro duction of PGE2 (Chen, et al., 2006). Increased PGE2 levels increase chronic inflammation and immune suppression, which then creates an environment suitable for tumor proliferation.

Cigarette smoke also activates the NF-κB pathway, which is an important regulator of inflammatory and oncogenic signaling (Bhoopathi, et al., 2010). Nicotine and NNK may activate toll-like receptors (TLRs) or other upstream receptors, resulting in the activation of NEMO, IKKα, and IKKβ, which eventually phosphorylate IκB, marking it for proteasomal destruction. This stimulates the translocation of NF-κB into the nucleus, where it enhances the transcription of many tumor-promoting proteins, including as VEGF, MMP-9, and cyclin D1 (Wong, et al., 2009). VEGF promotes angiogenesis, which allows the development of new blood vessels that deliver oxygen and nutrients to tumor cells (Onguru, et al., 2004). MMP-9 increases extracellular matrix disintegration which helps cancer cell invasion and metastasis while cyclin D1 drives uncontrolled cell proliferation which is an indicator of malignancy (Kamat, et al., 2009).

In addition to NF-κB, another critical pathway is affected by smoking is the TxA2-TP signaling pathway. TP receptors are activated by TxA2, which is a of COX-2 activity product (Onguru, et al., 2004). It triggers intracellular signaling pathways that encourage invasion, migration, and cell

survival. This pathway contributes to the increased penetrating capability of bladder cancer cells, which results accelerating disease progression.

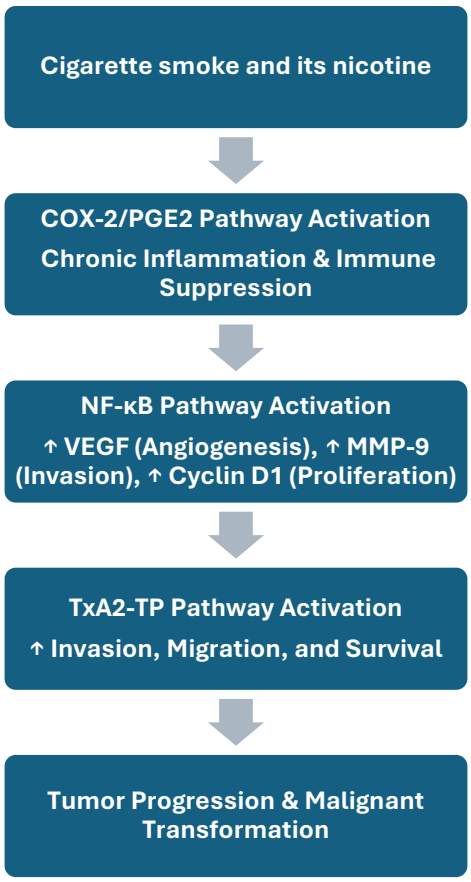

Figure 1: Cigarette smoke-induced TxA_2 imbalance promotes carcinogenesis using the signaling pathway COX-2/PGE2 Pathway Activation which cause by chronic inflammation and immune suppression.

These pathways work together to create a self-sustaining pro-tumorigenic environment in which chronic inflammation, oxidative stress, and DNA damage promote malignant transformation. constant activation of these signaling pathways highlights the serious characteristics of smoking-induced bladder cancer, indicating prospective treatment targets such COX-2 inhibitors and NF-κB pathway antagonists to reduce disease development.

Chapter 4

Protective Role of Garlic in Bladder Cancer

4.1 Bioactive Compounds in Garlic

One of the most beneficial foods for people's health, garlic (Allium sativum) has sulfur-containing chemicals that have anticancer effects among its many other advantages (Shang, et al.,2019). When garlic has been crushed or minced, its principal bioactive component, alliin, transforms into allicin. Because of its instability, allicin breaks down quickly into various sulfur-containing molecules like DADS, DATS, and S-allyl cysteine (Mondal, et al., 2022). By focusing on certain cancer markers, these chemicals show strong anticancer activity.

Both DADS and DATS are able to cross cell membranes and have an immediate impact on metabolic processes within cells (El-Saadony, et al., 2024). As a water-soluble molecule, SAC fights oxidative stress. It is a critical component in smoking-induced carcinogenesis. Research shows that these chemicals can repair DNA damage caused by carcinogens like aromatic amines in tobacco smoke in addition to neutralizing free radicals (Martins, et al., 2016). The lipophilic nature of DADS and DATS allows them to interact with lipid bilayers in cells, altering signaling pathways crucial for cancer progression (Mitra, et al., 2022). Furthermore, garlic's compounds enhance the immune system, activating natural killer (NK) cells. Because of its many cancer-fighting bioactive components, garlic is being considered as a potential dietary intervention that might reduce the impact of smoking on the urinary system (Pandey, et al., 2023).

Another important factor is garlic's ability to reduce inflammation. The microenvironment in the bladder is supportive to cancer development due to chronic inflammation, which is frequently grew more severe by smoking (Rauf, et al., 2022). Garlic lowers this risk by inhibiting inflammatory

pathways and cytokines (Miroddi, et al., 2011). The strong antioxidant activity of garlic is one mechanism by which it fights urinary adenocarcinoma. Garlic reduces the oxidative stress and DNA damage caused by smoking-related carcinogens by neutralizing free radicals (De Greef, et al., 2021). Tobacco metabolites in urine can cause cancer if exposed to the bladder for an extended period of time, making this process all the more important

4.2 Mechanisms of Cancer Prevention

The anticancer effects of garlic are exerted through multiple pathways that directly affect the vital processes that lead to the beginning and advancement of cancer.

There are a number of pathways that garlic uses to exert its anticancer effects, all of which aim at critical steps in the cancer life cycle (Riggs, et al., 1997). It’s one of the most well-documented effects is the induction of apoptosis. Bioactive sulfur compounds like DADS and SAC activate both intrinsic (mitochondria-mediated) and extrinsic (death receptor-mediated) apoptotic pathways (Lamm, et al., 2001). These methods ensure that only malignant cells are killed, without harming healthy ones. Additionally, garlic components stop the cell cycle in the G2/M and S stages (Kim, et al., 2010). Garlic stops cell division, which means cancer-causing mutant cells can't proliferate uncontrolled (Wang, et al., 2015). There is a rise of ROS in malignancies caused by smoking; however, garlic's antioxidant characteristics mitigate this effect. Garlic lowers mutation rates and DNA damage by decreasing oxidative stress (Marsh, et al., 1987). One of the most important mechanisms is that garlic helps reduce chronic inflammation, a common reason for cancer. Garlic lowers down the production of pro-inflammatory cytokines such as IL-6, TNF-α, and COX-2 (Kim, et al., 2018). The beginning of tumor and proliferation are slowed by this anti-inflammatory activity. Another process that garlic blocks is angiogenesis. By this process tumors get their oxygen and nutrition from new blood vessels. Studies shows that compounds like DATS have the ability to inhibit vascular endothelial growth factor (VEFG) (Kodali, et al., 2015). Garlic also stops cancer cells from spreading to other parts of the body by blocking matrix metalloproteinases (MMPs), by this MMPs cancer cell access nearby tissue. Collectively, these methods illustrate garlic's potential as a natural, multifunctional anticancer drug, especially in

reducing the carcinogenic impacts of smoking on the urinary system (Wang, et al., 2015) (Butt, et al., 2009).

4.3 Key Signaling Pathways

Bioactive substances in garlic have a major impact on cancer-related molecular signaling pathways. NF-κB, PI3K/AKT, and MAPK are pathways that are frequently activated in smoking-related carcinogenesis. In order to reduce the development of tumors, garlic acts on these mechanisms (Shin, et al., 2014). Cancers caused by smoking frequently have an overactive NF-κB pathway, which is a key regulator of inflammation and cancer. Compounds in garlic, like DADS and SAC, stop NF-κB from moving to the nucleus (Shin, et al., 2017). This stops the production of genes that cause inflammation and survival. Chronic inflammation is a key component of urinary adenocarcinoma, where this inhibition reduced it.

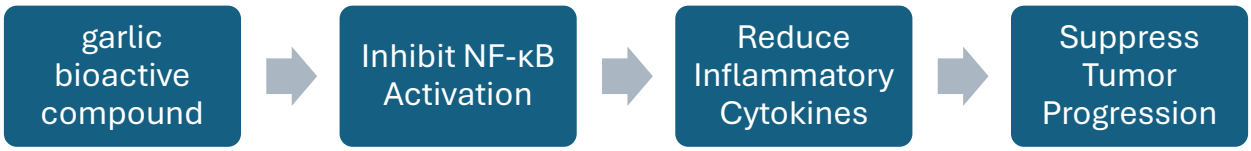

Figure 2 : NF-κB Pathway is inhibited by the compound like DADS and SAC which reduce inflammatory cytokine and leading tumor suppression

Garlic also targets the PI3K/AKT pathway, which is involved in cell survival and proliferation (Bassi, et al., 2008). Researchers have shown that chemicals in garlic can make cancer cells more prone to cell death by reducing phosphorylation of PI3K and AKT (Amagase, et al., 2001). Compounds of garlic inhibit those signals which are already increased by smoking carcinogens (Taylor, et al., 2009).

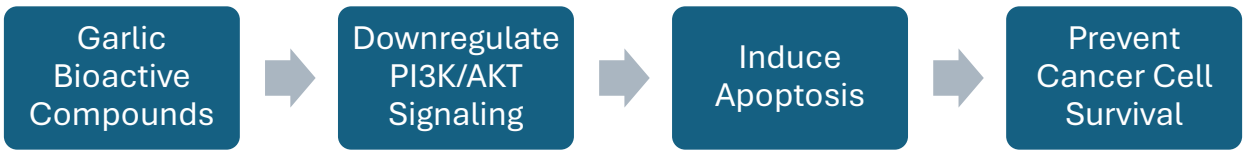

Figure 3: Garlic reducing phosphorylation of PI3K/AKT Pathway which will helps in apoptosis resulting cell death in controlled manner

Additionally, garlic also affects the MAPK pathway (Toker, et al., 2006). Which controls cell growth, differentiation, and apoptosis. In cancer cells, it has been found that DATS can block MAPK signaling, specifically the ERK and JNK sub-pathways (Wu, et al., 2009). This results in an increase of cell death while simultaneously limiting the spread of cancer cells.

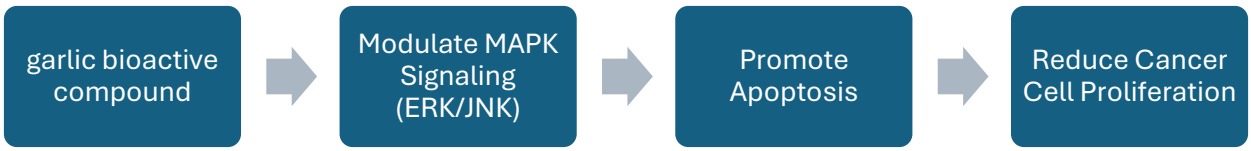

Figure 4 : Garlics effects on MAPK Pathway and Erk and JNK sub-pathway which will control the cell growth and apoptosis eventually resulting reduce cancer cell multiplication

Furthermore, garlic frequently increase the activity of tumor suppressor proteins like p53, which helps to reduce the activity of adenocarcinoma. Also, garlic helps to repair its damaged DNA by stabilizing and activating p53 (Kim, et al., 2017). Garlic is a potential therapy for the prevention of urinary adenocarcinoma due to its capacity to combat the pro-carcinogenic signals caused by smoking, which makes it a valuable agent for the prevention of urinary adenocarcinoma.

Chapter 5
Discussion

The result of this review strongly connects the correlation between smoking and urinary adenocarcinoma which highlight the molecular mechanism which may cause cancer. The role of aromatic amines, polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and reactive oxygen species (ROS) in causing DNA damage, oxidative stress, and chronic inflammation mentioned here. These mechanisms activate key carcinogenic pathways which includes NF-κB, COX-2/PGE2, and PI3K/AKT and leading to uncontrolled cell proliferation, inhibition of apoptosis, and increased metastasis. The combined effect of these molecular effect creates an environment for cancer development.

On the other hand, garlic shows its potential anticancer properties by its components like allicin, DADS, DATS, and S-allyl cysteine (SAC). These compounds reduce the carcinogenic effect caused by smoking by lower down oxidative stress, inhibiting pro-inflammatory pathways, and promoting apoptosis in cancer cells. Furthermore, garlic enhances the activity of tumor suppressor proteins like p53. Which helps to repair DNA damage and prevent malignant transformation.

These information's suggest that changes in diet may play a significant role in reducing the risk of smoking-related urinary adenocarcinoma. Although quitting smoking is the most effective preventive method where adding garlic into the diet may provide an extra protective strategy. These evidence of garlic's anticancer property suggests that further clinical and preclinical studies should focus on its use for cancer prevention. Future research should focus on developing stabilized garlic formulations with enhanced bioavailability to maximize its potential benefits.

Chapter 6
Conclusion

Smoking is now a common issue in all over the world. It is still one of the leading preventable causes of illness and early death globally. From above analysis, smoking is known to be a well-recognized and known risk factor for different types of cancer.

Smoking is a major risk factor for urinary adenocarcinoma, which appears to be a significant health concern in our daily life. Despite the widely reported adverse consequences of tobacco smoke, there is a growing interest in the organic and natural treatment to reduce its effects. This review highlights the need for proactive measures in both prevention and treatment strategies.

Garlic shows significant protective effects against smoking-related urinary adenocarcinoma. The bioactive compound of garlic has shown potential anticancer properties in this study. Further research's is necessary to stablish its role in adenocarcinoma prevention therapy.

Steps such as quitting smoking, and adding garlic consumption as part of dietary needs can reduce the chance of being affected. Furthermore, disease prevention strategies such as smoking bans and awareness campaigns are crucial. Lastly, research into garlic's molecular mechanisms may lead to new therapeutic approaches. Finally, initiatives must be taken to create standard formulations that improve garlic's bioavailability and therapeutic effectiveness. Together, dietary changes, lifestyle changes, and medical developments can lower the incidence of smoking-related malignancies and open the door to more effective strategies for both prevention and treatment of urinary adenocarcinoma.

Reference:

Alsaad, A. M., Al-Arifi, M. N., Maayah, Z. H., Attafi, I. M., Alanazi, F. E., Belali, O. M., Alhoshani, A., Asiri, Y. A., & Korashy, H. M. (2019). Genotoxic impact of long-term cigarette and waterpipe smoking on DNA damage and oxidative stress in healthy subjects. *Toxicology mechanisms and methods*, *29*(2), 119–127. https://doi.org/10.1080/15376516.2018.1528650

Al-Zalabani, A. H., Stewart, K. F. J., Wesselius, A., Schols, A. M. W. J., & Zeegers, M. P. (2016). Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. In *European Journal of Epidemiology* (Vol. 31, Issue 9, pp. 811–851). Springer Netherlands. https://doi.org/10.1007/s10654-016-0138-6

Amagase, H., Petesch, B. L., Matsuura, H., Kasuga, S., & Itakura, Y. (2001). Intake of garlic and its bioactive components. *The Journal of nutrition*, *131*(3s), 955S–62S. https://doi.org/10.1093/jn/131.3.955S

Anderson, B. (n.d.). Understanding the role of smoking in the aetiology of bladder cancer. In *British Journal of Community Nursing* (Vol. 14, Issue 9).

Banan, A., Zhang, L. J., Shaikh, M., Fields, J. Z., Farhadi, A., & Keshavarzian, A. (2004). Novel effect of NF-kappaB activation: carbonylation and nitration injury to cytoskeleton and disruption of monolayer barrier in intestinal epithelium. *American journal of physiology. Cell physiology*, *287*(4), C1139–C1151. https://doi.org/10.1152/ajpcell.00146.2004

Bassi, R., Heads, R., Marber, M. S., & Clark, J. E. (2008). Targeting p38-MAPK in the ischaemic heart: kill or cure?. *Current opinion in pharmacology*, *8*(2), 141–146. https://doi.org/10.1016/j.coph.2008.01.002

Bat-Chen, W., Golan, T., Peri, I., Ludmer, Z., & Schwartz, B. (2010). Allicin purified from fresh garlic cloves induces apoptosis in colon cancer cells via Nrf2. *Nutrition and cancer*, *62*(7), 947–957. https://doi.org/10.1080/01635581.2010.509837

Bhoopathi, P., Chetty, C., Gujrati, M., Dinh, D. H., Rao, J. S., & Lakka, S. S. (2010). The role of MMP-9 in the anti-angiogenic effect of secreted protein acidic and rich in cysteine. *British journal of cancer*, *102*(3), 530–540. https://doi.org/10.1038/sj.bjc.6605538

Boström, P. J., Aaltonen, V., Söderström, K. O., Uotila, P., & Laato, M. (2001). Expression of cyclooxygenase-1 and -2 in urinary bladder carcinomas in vivo and in vitro and prostaglandin E2 synthesis in cultured bladder cancer cells. *Pathology*, *33*(4), 469–474. https://doi.org/10.1080/00313020120083188

Brennan, P., Bogillot, O., Greiser, E., Chang-Claude, J., Rgen Wahrendorf, J., Cordier, S., Joè, K.-H., Lopez-Abente, G., Tzonou, A., Vineis, P., Donato, F., Hours, M., Serra, C., Bolm-Audor□, U., Schill, W., Kogevinas, M., & Bo□etta, P. (n.d.). *The contribution of cigarette smoking to bladder cancer in women (pooled European data)*.

Butt, M. S., Sultan, M. T., Butt, M. S., & Iqbal, J. (2009). Garlic: nature's protection against physiological threats. *Critical reviews in food science and nutrition*, *49*(6), 538–551. https://doi.org/10.1080/10408390802145344

Cadet, J., Douki, T., Gasparutto, D., & Ravanat, J. L. (2003). Oxidative damage to DNA: formation, measurement and biochemical features. *Mutation research*, *531*(1-2), 5–23. https://doi.org/10.1016/j.mrfmmm.2003.09.001

Cha, S. R., Jang, J., Park, S. M., Ryu, S. M., Cho, S. J., & Yang, S. R. (2023). Cigarette Smoke-Induced Respiratory Response: Insights into Cellular Processes and Biomarkers. In *Antioxidants* (Vol. 12, Issue 6). MDPI. https://doi.org/10.3390/antiox12061210

Chavan, S., Bray, F., Lortet-Tieulent, J., Goodman, M., & Jemal, A. (2014). International variations in bladder cancer incidence and mortality. *European urology*, *66*(1), 59–73. https://doi.org/10.1016/j.eururo.2013.10.001

Chen, G. G., Lee, T. W., Yip, J. H., Xu, H., Lee, I. K., Mok, T. S., Warner, T. D., & Yim, A. P. (2006). Increased thromboxane B(2) levels are associated with lipid peroxidation and Bcl-2 expression in human lung carcinoma. *Cancer letters*, *234*(2), 193–198. https://doi.org/10.1016/j.canlet.2005.03.032

Chevillard, S., Radicella, J. P., Levalois, C., Lebeau, J., Poupon, M. F., Oudard, S., Dutrillaux, B., & Boiteux, S. (1998). Mutations in OGG1, a gene involved in the repair of oxidative DNA damage, are found in human lung and kidney tumours. *Oncogene*, *16*(23), 3083–3086. https://doi.org/10.1038/sj.onc.1202096

Colquhoun AJ, Mellon JK. Epidermal growth factor receptor and bladder cancer. Postgrad Med J. 2002 Oct;78(924):584-9. doi: 10.1136/pmj.78.924.584. PMID: 12415079; PMCID: PMC1742539.

Danielsen, P. H., Bräuner, E. V., Barregard, L., Sällsten, G., Wallin, M., Olinski, R., Rozalski, R., Møller, P., & Loft, S. (2008). Oxidatively damaged DNA and its repair after experimental exposure to wood smoke in healthy humans. *Mutation research*, *642*(1-2), 37–42. https://doi.org/10.1016/j.mrfmmm.2008.04.001

De Greef, D., Barton, E. M., Sandberg, E. N., Croley, C. R., Pumarol, J., Wong, T. L., Das, N., & Bishayee, A. (2021). Anticancer potential of garlic and its bioactive constituents: A systematic and comprehensive review. *Seminars in cancer biology*, *73*, 219–264. https://doi.org/10.1016/j.semcancer.2020.11.020

El-Saadony, M. T., Saad, A. M., Korma, S. A., Salem, H. M., Abd El-Mageed, T. A., Alkafaas, S. S., Elsalahaty, M. I., Elkafas, S. S., Mosa, W. F. A., Ahmed, A. E., Mathew, B. T., Albastaki, N. A., Alkuwaiti, A. A., El-Tarabily, M. K., AbuQamar, S. F., El-Tarabily, K. A., & Ibrahim, S. A. (2024). Garlic bioactive substances and their therapeutic applications for improving human health: a comprehensive review. *Frontiers in immunology*, *15*, 1277074. https://doi.org/10.3389/fimmu.2024.1277074

England, K., O'Driscoll, C., & Cotter, T. G. (2004). Carbonylation of glycolytic proteins is a key response to drug-induced oxidative stress and apoptosis. *Cell death and differentiation*, *11*(3), 252–260. https://doi.org/10.1038/sj.cdd.4401338

European Standards Committee on Oxidative DNA Damage (ESCODD) (2003). Measurement of DNA oxidation in human cells by chromatographic and enzymic methods. *Free radical biology & medicine*, *34*(8), 1089–1099. https://doi.org/10.1016/s0891-5849(03)00041-8

Freedman, N. D., Debra Silverman, M. T., Albert Hollenbeck, S. R., Schatzkin, A., & Abnet, C. C. (n.d.). *Association Between Smoking and Risk of Bladder Cancer Among Men and Women*. http://jama.jamanetwork.com/

Gecit, İ., Eryılmaz, R., Kavak, S., Meral, İ., Demir, H., Pirinççi, N., Güneş, M., & Taken, K. (2017). The Prolidase Activity, Oxidative Stress, and Nitric Oxide Levels of Bladder Tissues with or

Without Tumor in Patients with Bladder Cancer. *The Journal of membrane biology*, *250*(5), 455–459. https://doi.org/10.1007/s00232-017-9971-0

Habib, S. H. M., Makpol, S., Hamid, N. A. A., Das, S., Ngah, W. Z. W., & Yusof, Y. A. M. (2008). Ginger extract (Zingiber officinale) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. *Clinics*, *63*(6), 807–813. https://doi.org/10.1590/S1807-59322008000600017

Hecht, S. S. (n.d.). *Tobacco Smoke Carcinogens and Lung Cancer*. http://jnci.oxfordjournals.org/

Hogg R. C. (2016). Contribution of Monoamine Oxidase Inhibition to Tobacco Dependence: A Review of the Evidence. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*, *18*(5), 509–523. https://doi.org/10.1093/ntr/ntv245

Huang, Run-Yue & Chen, George. (2010). Cigarette smoking, cyclooxygenase-2 pathway and cancer. Biochimica et biophysica acta. 1815. 158-69. 10.1016/j.bbcan.2010.11.005.

Hudson, J. D., Shoaibi, M. A., Maestro, R., Carnero, A., Hannon, G. J., & Beach, D. H. (1999). A proinflammatory cytokine inhibits p53 tumor suppressor activity. *The Journal of experimental medicine*, *190*(10), 1375–1382. https://doi.org/10.1084/jem.190.10.1375

Hui, S. C., Wang, Z., Zhang, H., & Ogle, C. W. (1992). Arachidonic acid metabolism in nicotine-treated rats and nicotine-incubated rabbit aortic smooth muscle cells. *Clinical and experimental pharmacology & physiology*, *19*(10), 689–693. https://doi.org/10.1111/j.1440-1681.1992.tb00405.x

Islam, M. O., Bacchetti, T., & Ferretti, G. (2019). Alterations of Antioxidant Enzymes and Biomarkers of Nitro-oxidative Stress in Tissues of Bladder Cancer. *Oxidative medicine and cellular longevity*, *2019*, 2730896. https://doi.org/10.1155/2019/2730896

Jha, P., & Peto, R. (2014). Global Effects of Smoking, of Quitting, and of Taxing Tobacco. *New England Journal of Medicine*, *370*(1), 60–68. https://doi.org/10.1056/nejmra1308383

Jiang, T., Huang, Z., Chan, J. Y., & Zhang, D. D. (2009). Nrf2 protects against As(III)-induced damage in mouse liver and bladder. *Toxicology and applied pharmacology*, *240*(1), 8–14. https://doi.org/10.1016/j.taap.2009.06.010

Kamat, A. M., Sethi, G., & Aggarwal, B. B. (2007). Curcumin potentiates the apoptotic effects of chemotherapeutic agents and cytokines through down-regulation of nuclear factor-kappaB and nuclear factor-kappaB-regulated gene products in IFN-alpha-sensitive and IFN-alpha-resistant human bladder cancer cells. *Molecular cancer therapeutics*, *6*(3), 1022–1030. https://doi.org/10.1158/1535-7163.MCT-06-0545

Kim, W. J., Kim, E. J., Kim, S. K., Kim, Y. J., Ha, Y. S., Jeong, P., Kim, M. J., Yun, S. J., Lee, K. M., Moon, S. K., Lee, S. C., Cha, E. J., & Bae, S. C. (2010). Predictive value of progression-related gene classifier in primary non-muscle invasive bladder cancer. *Molecular cancer*, *9*, 3. https://doi.org/10.1186/1476-4598-9-3

Kim, W. T., Seo, S. P., Byun, Y. J., Kang, H. W., Kim, Y. J., Lee, S. C., Jeong, P., Song, H. J., Choe, S. Y., Kim, D. J., Kim, S. K., Ha, Y. S., Moon, S. K., Lee, G. T., Kim, I. Y., Yun, S. J., & Kim, W. J. (2018). The Anticancer Effects of Garlic Extracts on Bladder Cancer Compared to Cisplatin: A Common Mechanism of Action via Centromere Protein M. *The American journal of Chinese medicine*, *46*(3), 689–705. https://doi.org/10.1142/S0192415X18500362

Kim, W. T., Seo, S. P., Byun, Y. J., Kang, H. W., Kim, Y. J., Lee, S. C., Jeong, P., Seo, Y., Choe, S. Y., Kim, D. J., Kim, S. K., Moon, S. K., Choi, Y. H., Lee, G. T., Kim, I. Y., Yun, S. J., & Kim, W. J. (2017). Garlic extract in bladder cancer prevention: Evidence from T24 bladder cancer cell xenograft model, tissue microarray, and gene network analysis. *International journal of oncology*, *51*(1), 204–212. https://doi.org/10.3892/ijo.2017.3993

Kodali, R. T., & Eslick, G. D. (2015). Meta-analysis: Does garlic intake reduce risk of gastric cancer?. *Nutrition and cancer*, *67*(1), 1–11. https://doi.org/10.1080/01635581.2015.967873

Kodali, R. T., & Eslick, G. D. (2015). Meta-analysis: Does garlic intake reduce risk of gastric cancer?. *Nutrition and cancer*, *67*(1), 1–11. https://doi.org/10.1080/01635581.2015.967873

Kömhoff, M., Guan, Y., Shappell, H. W., Davis, L., Jack, G., Shyr, Y., Koch, M. O., Shappell, S. B., & Breyer, M. D. (2000). Enhanced expression of cyclooxygenase-2 in high grade human transitional cell bladder carcinomas. *The American journal of pathology*, *157*(1), 29–35. https://doi.org/10.1016/S0002-9440(10)64513-0

Lamm, D. L., & Riggs, D. R. (2001). Enhanced immunocompetence by garlic: role in bladder cancer and other malignancies. *The Journal of nutrition*, *131*(3s), 1067S–70S. https://doi.org/10.1093/jn/131.3.1067S

Liou, G. Y., & Storz, P. (2010). Reactive oxygen species in cancer. *Free radical research*, *44*(5), 479–496. https://doi.org/10.3109/10715761003667554

Marsh, C. L., Torrey, R. R., Woolley, J. L., Barker, G. R., & Lau, B. H. (1987). Superiority of intravesical immunotherapy with Corynebacterium parvum and Allium sativum in control of murine bladder cancer. *The Journal of urology*, *137*(2), 359–362. https://doi.org/10.1016/s0022-5347(17)44023-7

Martins, N., Petropoulos, S., & Ferreira, I. C. (2016). Chemical composition and bioactive compounds of garlic (Allium sativum L.) as affected by pre- and post-harvest conditions: A review. *Food chemistry*, *211*, 41–50. https://doi.org/10.1016/j.foodchem.2016.05.029

Miroddi, M., Calapai, F., & Calapai, G. (2011). Potential beneficial effects of garlic in oncohematology. *Mini reviews in medicinal chemistry*, *11*(6), 461–472. https://doi.org/10.2174/138955711795843293

Mitra, S., Das, R., Emran, T. B., Labib, R. K., Noor-E-Tabassum, Islam, F., Sharma, R., Ahmad, I., Nainu, F., Chidambaram, K., Alhumaydhi, F. A., Chandran, D., Capasso, R., & Wilairatana, P. (2022). Diallyl Disulfide: A Bioactive Garlic Compound with Anticancer Potential. *Frontiers in pharmacology*, *13*, 943967. https://doi.org/10.3389/fphar.2022.943967

Mondal, A., Banerjee, S., Bose, S., Mazumder, S., Haber, R. A., Farzaei, M. H., & Bishayee, A. (2022). Garlic constituents for cancer prevention and therapy: From phytochemistry to novel formulations. *Pharmacological research*, *175*, 105837. https://doi.org/10.1016/j.phrs.2021.105837

Moon, S. K., Cha, B. Y., & Kim, C. H. (2004). ERK1/2 mediates TNF-alpha-induced matrix metalloproteinase-9 expression in human vascular smooth muscle cells via the regulation of NF-kappaB and AP-1: Involvement of the ras dependent pathway. *Journal of cellular physiology*, *198*(3), 417–427. https://doi.org/10.1002/jcp.10435

Onguru, O., Scheithauer, B. W., Kovacs, K., Vidal, S., Jin, L., Zhang, S., Ruebel, K. H., & Lloyd, R. V. (2004). Analysis of Cox-2 and thromboxane synthase expression in pituitary adenomas and carcinomas. *Endocrine pathology*, *15*(1), 17–27. https://doi.org/10.1385/ep:15:1:17

Onguru, O., Scheithauer, B. W., Kovacs, K., Vidal, S., Jin, L., Zhang, S., Ruebel, K. H., & Lloyd, R. V. (2004). Analysis of Cox-2 and thromboxane synthase expression in pituitary adenomas and carcinomas. *Endocrine pathology*, *15*(1), 17–27. https://doi.org/10.1385/ep:15:1:17

Pandey, P., Khan, F., Alshammari, N., Saeed, A., Aqil, F., & Saeed, M. (2023). Updates on the anticancer potential of garlic organosulfur compounds and their nanoformulations: Plant therapeutics in cancer management. *Frontiers in pharmacology*, *14*, 1154034. https://doi.org/10.3389/fphar.2023.1154034

Pang, L. Y., Hurst, E. A., & Argyle, D. J. (2016). Cyclooxygenase-2: A Role in Cancer Stem Cell Survival and Repopulation of Cancer Cells during Therapy. *Stem cells international*, *2016*, 2048731. https://doi.org/10.1155/2016/2048731

Patchsung, M., Boonla, C., Amnattrakul, P., Dissayabutra, T., Mutirangura, A., & Tosukhowong, P. (2012). Long interspersed nuclear element-1 hypomethylation and oxidative stress: correlation and bladder cancer diagnostic potential. *PloS one*, *7*(5), e37009. https://doi.org/10.1371/journal.pone.0037009

Popov, H., Stoyanov, G. S., & Ghenev, P. (2023). Intestinal-Type Adenocarcinoma of the Urinary Bladder With Coexisting Cystitis Cystica et Glandularis and Intestinal Metaplasia: A Histopathological Case Report. *Cureus*. https://doi.org/10.7759/cureus.36554

Ranasinghe, W. K., De Silva, D., De Silva, M. V., Ranasinghe, T. I., Lawrentschuk, N., Bolton, D., & Persad, R. (2012). Incidence of bladder cancer in sri lanka: analysis of the cancer registry data and review of the incidence of bladder cancer in the South asian population. *Korean journal of urology*, *53*(5), 304–309. https://doi.org/10.4111/kju.2012.53.5.304

Rauf, A., Abu-Izneid, T., Thiruvengadam, M., Imran, M., Olatunde, A., Shariati, M. A., Bawazeer, S., Naz, S., Shirooie, S., Sanches-Silva, A., Farooq, U., & Kazhybayeva, G. (2022). Garlic (Allium sativum L.): Its Chemistry, Nutritional Composition, Toxicity, and Anticancer Properties. *Current topics in medicinal chemistry*, *22*(11), 957–972. https://doi.org/10.2174/1568026621666211105094939

Raziuddin, S., Masihuzzaman, M., Shetty, S., & Ibrahim, A. (1993). Tumor necrosis factor alpha production in schistosomiasis with carcinoma of urinary bladder. *Journal of clinical immunology*, *13*(1), 23–29. https://doi.org/10.1007/BF00920632

Reszka, E., Lesicka, M., Wieczorek, E., Jabłońska, E., Janasik, B., Stępnik, M., Konecki, T., & Jabłonowski, Z. (2020). Dysregulation of Redox Status in Urinary Bladder Cancer Patients. *Cancers*, *12*(5), 1296. https://doi.org/10.3390/cancers12051296

Reuter, S., Gupta, S. C., Chaturvedi, M. M., & Aggarwal, B. B. (2010). Oxidative stress, inflammation, and cancer: how are they linked?. *Free radical biology & medicine*, *49*(11), 1603–1616. https://doi.org/10.1016/j.freeradbiomed.2010.09.006

Richters, A., Aben, K. K. H., & Kiemeney, L. A. L. M. (2020). The global burden of urinary bladder cancer: an update. *World journal of urology*, *38*(8), 1895–1904. https://doi.org/10.1007/s00345-019-02984-4

Riggs, D. R., DeHaven, J. I., & Lamm, D. L. (1997). Allium sativum (garlic) treatment for murine transitional cell carcinoma. *Cancer*, *79*(10), 1987–1994. https://doi.org/10.1002/(sici)1097-0142(19970515)79:10<1987::aid-cncr21>3.0.co;2-q

Roy, S., & Parwani, A. V. (2011). Adenocarcinoma of the urinary bladder. In *Archives of Pathology and Laboratory Medicine* (Vol. 135, Issue 12, pp. 1601–1605). https://doi.org/10.5858/arpa.2009-0713-RS

Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci (Basel). 2020 Mar 13;8(1):15. doi: 10.3390/medsci8010015. PMID: 32183076; PMCID: PMC7151633.

Savina, N. V., Nikitchenko, N. V., Kuzhir, T. D., Rolevich, A. I., Krasny, S. A., & Goncharova, R. I. (2016). The Cellular Response to Oxidatively Induced DNA Damage and Polymorphism of Some DNA Repair Genes Associated with Clinicopathological Features of Bladder Cancer. *Oxidative medicine and cellular longevity*, *2016*, 5710403. https://doi.org/10.1155/2016/5710403

Sawicka, E., Lisowska, A., Kowal, P., & Długosz, A. (2015). Rola stresu oksydacyjnego w raku pęcherza moczowego [The role of oxidative stress in bladder cancer]. *Postepy higieny i medycyny doswiadczalnej (Online)*, *69*, 744–752. https://doi.org/10.5604/17322693.1160361

Shang, A., Cao, S. Y., Xu, X. Y., Gan, R. Y., Tang, G. Y., Corke, H., Mavumengwana, V., & Li, H. B. (2019). Bioactive Compounds and Biological Functions of Garlic (*Allium sativum* L.). *Foods (Basel, Switzerland)*, *8*(7), 246. https://doi.org/10.3390/foods8070246

Shin, D. Y., Kim, G. Y., Hwang, H. J., Kim, W. J., & Choi, Y. H. (2014). Diallyl trisulfide-induced apoptosis of bladder cancer cells is caspase-dependent and regulated by PI3K/Akt and JNK pathways. *Environmental toxicology and pharmacology*, *37*(1), 74–83. https://doi.org/10.1016/j.etap.2013.11.002

Shin, S. S., Song, J. H., Hwang, B., Noh, D. H., Park, S. L., Kim, W. T., Park, S. S., Kim, W. J., & Moon, S. K. (2017). HSPA6 augments garlic extract-induced inhibition of proliferation, migration, and invasion of bladder cancer EJ cells; Implication for cell cycle dysregulation, signaling pathway alteration, and transcription factor-associated MMP-9 regulation. *PloS one*, *12*(2), e0171860. https://doi.org/10.1371/journal.pone.0171860

Sui, X., Lei, L., Chen, L., Xie, T., & Li, X. (2017). Inflammatory microenvironment in the initiation and progression of bladder cancer. *Oncotarget*, *8*(54), 93279–93294. https://doi.org/10.18632/oncotarget.21565

Taylor, J. A., 3rd, & Kuchel, G. A. (2009). Bladder cancer in the elderly: clinical outcomes, basic mechanisms, and future research direction. *Nature clinical practice. Urology*, *6*(3), 135–144. https://doi.org/10.1038/ncpuro1315

Toker, A., & Yoeli-Lerner, M. (2006). Akt signaling and cancer: surviving but not moving on. *Cancer research*, *66*(8), 3963–3966. https://doi.org/10.1158/0008-5472.CAN-06-0743

United States, Public Health Service. Office of the Surgeon General. (2010). How tobacco smoke causes disease; the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General.

Wang, W., Cheng, J., & Zhu, Y. (2015). The JNK Signaling Pathway Is a Novel Molecular Target for S-Propargyl- L-Cysteine, a Naturally-Occurring Garlic Derivatives: Link to Its Anticancer Activity in Pancreatic Cancer In Vitro and In Vivo. *Current cancer drug targets*, *15*(7), 613–623. https://doi.org/10.2174/1568009615666150602143943

Wigner, P., Bijak, M., & Saluk-bijak, J. (2021). The green anti-cancer weapon. The role of natural compounds in bladder cancer treatment. In *International Journal of Molecular Sciences* (Vol. 22, Issue 15). MDPI. https://doi.org/10.3390/ijms22157787

Wigner, P., Grębowski, R., Bijak, M., Saluk-Bijak, J., & Szemraj, J. (2021). The Interplay between Oxidative Stress, Inflammation and Angiogenesis in Bladder Cancer Development. *International journal of molecular sciences*, *22*(9), 4483. https://doi.org/10.3390/ijms22094483

Wong, H. P., Li, Z. J., Shin, V. Y., Tai, E. K., Wu, W. K., Yu, L., & Cho, C. H. (2009). Effects of cigarette smoking and restraint stress on human colon tumor growth in mice. *Digestion*, *80*(4), 209–214. https://doi.org/10.1159/000231898

Wu, X. J., Hu, Y., Lamy, E., & Mersch-Sundermann, V. (2009). Apoptosis induction in human lung adenocarcinoma cells by oil-soluble allyl sulfides: triggers, pathways, and modulators. *Environmental and molecular mutagenesis*, *50*(3), 266–275. https://doi.org/10.1002/em.20467