Exploring the Therapeutic Potential of Natural Flavanones in Lung and Colorectal Cancer Treatment

A project report presented to the Department of Pharmacy at Daffodil International University in partial fulfillment of the requirements for the Bachelor of Pharmacy degree.

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This project, submitted to the Department of Pharmacy, Faculty of Allied Health Science at Daffodil International University, has been deemed satisfactory for the partial fulfillment of the requirements for the Bachelor of Pharmacy (B.Pharm) degree. It is also approved for its style and content.

BOARD OF EXAMINERS

Professor Dr. Muniruddin Ahamed

Professor & Head

Department of Pharmacy

Faculty of Health & Life Sciences

Daffodil International University

..... **Internal Examiner-1**

..... **Internal Examiner-2**

..... **External Examiner**

Declaration

I confirm that I autonomously authored and concluded this project report to meet the criteria for the Bachelor of Pharmacy (B.Pharm) degree. The research was carried out under the supervision of Md. Sadman Hasib, Lecturer of the Department of Pharmacy at the Faculty of Allied Health Sciences, Daffodil International University. I assert my sole authorship of this project and assure that neither this work nor any of its components have been previously submitted to any other university for the purpose of obtaining a Bachelor's degree or any other academic qualification.

Supervised By:

Md. Sadman Hasib

Lecturer

Department of Pharmacy

Faculty of Health & Life Sciences

Daffodil International University

Submitted By:

Md. Rashedul Islam Jony

ID: 201-29-349

Department of Pharmacy

Faculty of Health & Life Sciences

Daffodil International University

Acknowledgement

I express my appreciation to the Almighty for granting me the health and resilience necessary to accomplish this endeavor.

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I would like to express my thanks to the entire faculty of the department for their consistent encouragement and support. Additionally, heartfelt appreciation goes to my parents for their unwavering support, love, and guidance.

My gratitude encompasses everyone who has contributed, either directly or indirectly, to the triumph of this project.

Md. Rashedul Islam Jony

Author,

Dedication

This endeavor is dedicated primarily to the Almighty, followed by my parents, instructors, and friends.

Abstract

This comprehensive review delves into the therapeutic potential of natural flavanones in the context of lung and colorectal cancer treatment. Exploring diverse facets, we elucidate the biological significance of flavanones, showcasing their antioxidant and anti-inflammatory properties. Unraveling intricate mechanisms of action, our focus extends to angiogenesis inhibition, apoptosis induction, and molecular pathway modulation, unveiling flavanones as versatile agents in cancer therapy. Investigating dietary sources and intake, we navigate the incorporation of flavanones into prevention and treatment strategies through both natural sources and supplements. Preclinical studies highlight flavanones' impact on lung cancer, inhibiting growth, proliferation, and inflammation, offering promise for clinical translation. Similarly, flavanones exhibit anti-colorectal cancer properties, modulating key pathways, inducing apoptosis, and inhibiting metastasis, accentuating their potential in addressing a leading cause of cancer-related mortality. Examining synergistic effects with chemotherapy, flavanones showcase the prospect of enhancing efficacy while minimizing side effects, laying the foundation for combination therapies. Biomarkers integrated into flavanone-based treatments emerge as a predictive tool, enabling personalized and targeted therapeutic strategies. Within the tumor microenvironment, flavanones demonstrate immunomodulatory effects, enhancing the anti-cancer immune response for sustained therapeutic benefits. This study serves as a roadmap for future investigations, fostering optimism for the integration of flavanones into precision medicine and personalized oncology interventions.

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CHAPTER ONE

INTRODUCTION

1.0 Introduction

Cancer, a complex and multifaceted group of diseases, continues to pose a formidable challenge to global public health. The relentless pursuit of effective and sustainable treatment modalities has driven researchers to explore the therapeutic potential of natural compounds. Among these, flavanones, a subgroup of polyphenolic compounds abundantly found in various fruits and vegetables, have emerged as promising candidates for cancer treatment [1]. With lung and colorectal cancers ranking among the leading causes of cancer-related morbidity and mortality worldwide, the exploration of novel therapeutic avenues becomes not only a scientific imperative but a pressing societal need. Flavanones, known for their diverse biological activities, encompass a spectrum of health-promoting properties. Derived from plant sources such as citrus fruits, tomatoes, and herbs, these compounds have long been recognized for their antioxidant, anti-inflammatory, and anti-cancer effects [2]. As the understanding of cancer biology deepens, researchers have turned their focus to unraveling the intricate mechanisms by which flavanones exert their therapeutic influence, with a particular emphasis on lung and colorectal cancers. The biological significance of flavanones extends beyond their antioxidant properties, encompassing a multifaceted array of activities that make them appealing candidates for cancer therapy. This comprehensive review aims to explore the intricate landscape of flavanones, beginning with an examination of their biological significance [3]. From modulating cellular signaling pathways to influencing gene expression patterns, flavanones navigate the complex terrain of cancer biology, presenting a compelling case for their potential as agents that extend beyond mere symptom management. Understanding the mechanisms of action is paramount in deciphering how flavanones intervene in cancer progression. From inhibiting angiogenesis—the formation of new blood vessels that nourish tumors—to inducing apoptosis—the programmed cell death essential for maintaining cellular homeostasis—flavanones showcase a multifaceted approach that positions them as formidable contenders in the battle against lung and colorectal cancers [4]. Unraveling these intricate molecular pathways not only sheds light on flavanones' anti-cancer potential but also provides a foundation for the development of targeted and personalized therapeutic strategies. While dietary sources play a crucial role in flavanone intake, challenges in obtaining therapeutic doses through diet alone underscore the potential significance of supplements in cancer prevention and treatment [5]. This review will delve into the dietary sources and intake of flavanones, exploring how these compounds can be harnessed to augment existing cancer prevention and

treatment strategies. By understanding the interplay between dietary choices, flavanone intake, and cancer outcomes, researchers can optimize nutritional interventions for enhanced efficacy. Preclinical studies investigating the impact of natural flavanones on lung cancer have yielded promising results. Flavanones have demonstrated the ability to inhibit the growth and proliferation of lung cancer cells, suggesting a potential role in suppressing tumor progression [6]. Additionally, flavanones exhibit anti-inflammatory effects, reducing the risk of cancer development in the lungs. This review will scrutinize the findings of these preclinical studies, providing a detailed examination of flavanones' impact on lung cancer and laying the groundwork for potential translational applications in clinical settings. Colorectal cancer, characterized by its high incidence and mortality rates, has also been a focal point in flavanone research. Studies have shown that flavanones possess anti-colorectal cancer properties by modulating key molecular pathways involved in tumorigenesis [7]. These compounds have demonstrated the ability to induce apoptosis in colorectal cancer cells and inhibit the metastatic potential of the disease. This review will meticulously explore the evidence surrounding flavanones' impact on colorectal cancer, offering insights into their therapeutic potential in mitigating one of the most prevalent forms of cancer. As research in the field progresses, one area that holds immense promise is the exploration of synergistic effects between natural flavanones and traditional chemotherapy agents. This review will delve into preclinical and clinical studies investigating the combined impact of flavanones and chemotherapy, emphasizing their potential to enhance efficacy while minimizing side effects [8]. By unraveling the intricate interplay between these natural compounds and conventional cancer treatments, researchers can pave the way for more comprehensive and effective therapeutic regimens. Moreover, the integration of biomarkers into the landscape of flavanone-based treatments represents a transformative approach, poised to usher in an era of personalized and targeted therapeutic strategies in cancer treatment. This review will investigate the use of biomarkers to predict patient response to flavanone-based treatments, paving the way for personalized and targeted therapeutic strategies [9]. Biomarkers, measurable indicators reflecting the biological state of an individual, hold the key to predicting patient response to flavanone interventions. The intricate interplay between flavanones and the immune system presents another layer of complexity in their potential therapeutic applications. This review will explore the immunomodulatory effects of flavanones within the tumor microenvironment, highlighting their role in enhancing the anti-cancer immune response for sustained therapeutic benefits. By

deciphering the molecular interactions between flavanones and immune cells, researchers can unlock new avenues for harnessing the body's natural defenses against cancer. Despite the exciting potential of natural flavanones, challenges such as bioavailability, dosage optimization, and patient variability need to be addressed [10]. Future research should focus on refining formulations and conducting large-scale clinical trials to establish the true therapeutic potential of flavanones in lung and colorectal cancer treatment. By unraveling these challenges and exploring the untapped dimensions of flavanones in cancer therapy, researchers can usher in a new era of precision medicine and personalized interventions, offering renewed hope for patients facing the complexities of lung and colorectal cancers. Through a comprehensive and multidimensional exploration, this review aspires to contribute to the evolving landscape of cancer treatment, shedding light on the untapped potential of flavanones as nature's allies in the fight against one of humanity's most formidable adversaries [11].

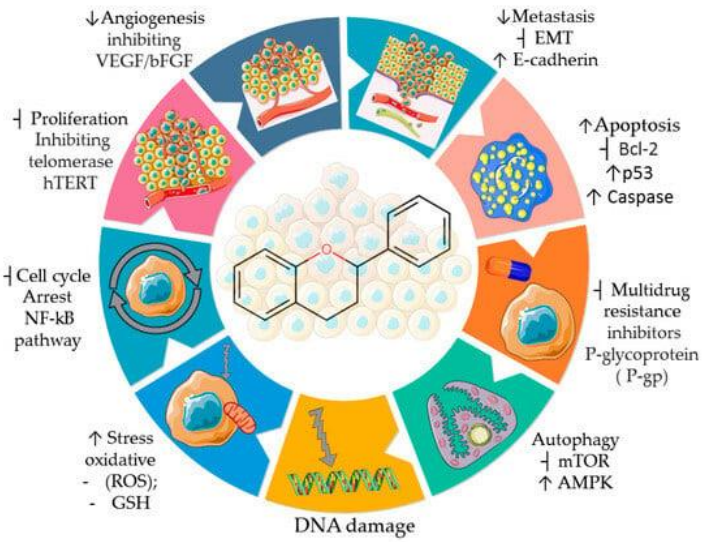


Figure-1.1: Characteristics, certain mechanisms of anticancer action exhibited by flavonoids [7].

1.1 Biological Significance of Flavanones

Flavanones, a subclass of flavonoids, stand as intriguing polyphenolic compounds celebrated for their multifaceted biological significance [12]. This detailed exploration will navigate through the intricate world of flavanones, unveiling their antioxidant, anti-inflammatory, and anti-cancer properties. Derived primarily from plant sources, including citrus fruits like oranges and

grapefruits, tomatoes, and various herbs, flavanones have captivated the interest of researchers and health enthusiasts alike for their potential therapeutic applications in cancer therapy and beyond.

Structural Basis and Diversity: At its core, flavanones are structurally characterized by a 15-carbon backbone, composed of two benzene rings (A and B) linked by a heterocyclic pyran ring (C). This unique arrangement imparts distinct chemical properties, contributing to their biological activities. The diversity of flavanones arises from substitutions on these rings, leading to a variety of compounds with nuanced effects [13].

Antioxidant Properties: One of the hallmarks of flavanones is their potent antioxidant activity. In the realm of cellular health, oxidative stress, stemming from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, plays a pivotal role in various diseases, including cancer. Flavanones, armed with their antioxidant prowess, neutralize ROS, thereby mitigating oxidative damage to cellular components such as DNA, proteins, and lipids [14].

The antioxidant capacity of flavanones extends beyond direct scavenging of free radicals; they also exhibit the ability to regenerate other antioxidants, such as vitamin C and vitamin E. This intricate interplay enhances the cellular defense mechanisms, reinforcing the cellular environment against oxidative insults [15].

Anti-Inflammatory Effects: Inflammation, a fundamental response to injury or infection, becomes problematic when chronic or unresolved, contributing to the development and progression of various diseases, including cancer. Flavanones have demonstrated remarkable anti-inflammatory effects by modulating key inflammatory pathways [16].

These compounds inhibit the activity of pro-inflammatory enzymes, such as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), which are involved in the synthesis of inflammatory mediators. Additionally, flavanones interfere with the production of inflammatory cytokines, pivotal molecules orchestrating the inflammatory response. By dampening these inflammatory signals, flavanones contribute to the maintenance of a balanced and controlled inflammatory environment [17].

Anti-Cancer Properties: Perhaps the most intriguing aspect of flavanones lies in their potential as anti-cancer agents. Extensive research has uncovered their ability to impede various stages of cancer development through diverse mechanisms [18].

- **Cell Cycle Regulation:** Flavanones exert control over the cell cycle, the orderly sequence of events governing cell division. By influencing cyclins and cyclin-dependent kinases, flavanones induce cell cycle arrest, preventing uncontrolled cell proliferation—a hallmark of cancer [19].
- **Apoptosis Induction:** The programmed cell death mechanism, known as apoptosis, plays a critical role in eliminating damaged or aberrant cells. Flavanones have been shown to induce apoptosis in cancer cells, triggering a cascade of molecular events that lead to the orderly demise of the aberrant cells [20].
- **Angiogenesis Inhibition:** Tumor growth is dependent on the formation of new blood vessels, a process called angiogenesis. Flavanones interfere with this crucial step by inhibiting the expression of pro-angiogenic factors, thereby limiting the blood supply to the growing tumor [21].
- **Metastasis Suppression:** Metastasis, the spread of cancer cells to distant sites, is a major challenge in cancer treatment. Flavanones have demonstrated anti-metastatic properties by inhibiting the migration and invasion of cancer cells, crucial steps in the metastatic cascade [22].

Plant Sources and Dietary Importance: Flavanones, although available in a variety of plant sources, are particularly abundant in citrus fruits, including oranges, lemons, and grapefruits. The peel of these fruits, often overlooked, is particularly rich in flavanones. Tomatoes, especially in their unripe state, and various herbs like parsley and thyme also contribute to the dietary intake of flavanones [23].

The dietary importance of flavanones is underscored by their potential health benefits. A diet rich in flavanone-containing foods has been associated with a lower risk of chronic diseases, including certain types of cancer. However, the challenge lies in achieving therapeutic doses solely through dietary means, leading to considerations of flavanone supplements in certain contexts [24].

Bioavailability and Metabolism: The journey of flavanones within the human body involves absorption, distribution, metabolism, and excretion, collectively known as pharmacokinetics. While the bioavailability of flavanones is influenced by factors such as food matrix and individual variations, their metabolic fate involves enzymatic transformations, particularly in the liver [25].
Phase I metabolism involves reactions such as hydroxylation and O-demethylation, altering the chemical structure of flavanones. Phase II metabolism includes conjugation processes, where the modified flavanones are coupled with water-soluble molecules to facilitate excretion. Understanding the intricate pharmacokinetics of flavanones is essential for optimizing their therapeutic potential [26].

Challenges and Considerations: Despite the promising attributes of flavanones, challenges exist in translating their potential into clinical applications. Issues such as bioavailability, dosage optimization, and patient variability require careful consideration. The formulation of flavanone supplements, addressing these challenges, becomes pivotal for ensuring consistent and efficacious delivery in cancer therapy [27].
Flavanones stand as remarkable polyphenolic compounds with a rich tapestry of biological activities. From their antioxidant and anti-inflammatory effects to their potential as anti-cancer agents, flavanones offer a multifaceted approach to promoting health and combatting diseases. As the exploration continues, flavanones remain a beacon of hope in the realm of natural compounds with profound implications for human health [28].

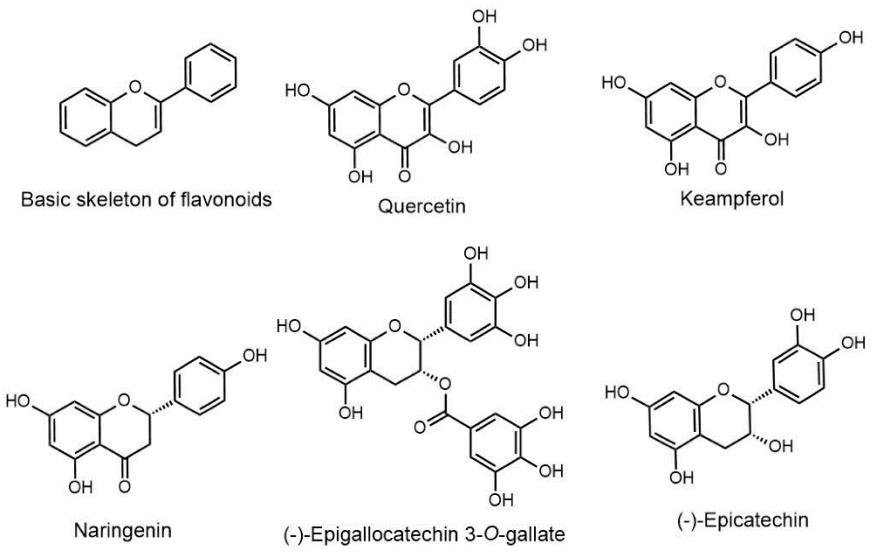


Figure-1.2: Graphical structure of different Flavonoid [29].

1.2 Mechanisms of Action

The mechanisms of action underlying the potent anti-cancer properties of natural flavanones are intricate and multifaceted, offering a promising strategy against the progression of lung and colorectal cancers. One of the pivotal avenues through which flavanones exert their influence is by inhibiting angiogenesis, a process crucial for sustained tumor growth and metastasis [30]. Angiogenesis, the formation of new blood vessels, is a hallmark of cancer progression, ensuring a continuous supply of nutrients and oxygen to the growing tumor. Flavanones disrupt this orchestrated process by targeting key pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). The downregulation of these factors impedes the formation of new blood vessels, effectively cutting off the tumor's lifeblood and thwarting its relentless expansion [31].

In addition to their anti-angiogenic effects, flavanones orchestrate a symphony of molecular events that culminate in the induction of apoptosis—the programmed cell death crucial for maintaining cellular homeostasis. This intricate mechanism serves as a biological fail-safe, eliminating aberrant cells and preventing uncontrolled proliferation, a hallmark of cancer. Flavanones leverage various signaling pathways to activate the apoptotic cascade, including the intrinsic mitochondrial pathway and the extrinsic death receptor pathway [32]. Within the mitochondria, flavanones modulate the

balance of pro-apoptotic and anti-apoptotic proteins, leading to the release of cytochrome c and the initiation of apoptosis. Simultaneously, engagement with death receptors on the cell surface triggers a cascade of events culminating in caspase activation and cellular demise. The ability of flavanones to navigate these intricate pathways highlights their potential as orchestrators of controlled cellular self-destruction, essential for impeding cancer progression [33].

Furthermore, flavanones exhibit a remarkable influence on the regulation of the cell cycle, a highly orchestrated sequence of events governing cell division. Dysregulation of the cell cycle is a characteristic feature of cancer cells, enabling uncontrolled proliferation. Flavanones intervene in this process by modulating key regulators such as cyclins and cyclin-dependent kinases (CDKs). By inducing cell cycle arrest at specific checkpoints, flavanones impose a regulatory checkpoint on the rapid division of cancer cells, preventing their unbridled growth. This nuanced modulation of the cell cycle underscores the precision with which flavanones navigate the molecular intricacies of cancer progression [34].

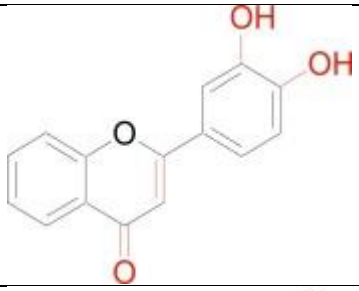
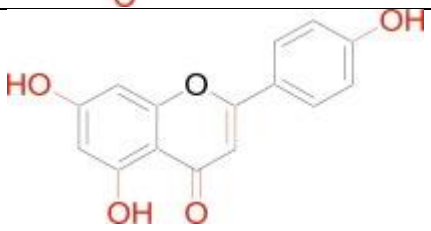
Beyond their direct impact on cancer cells, flavanones engage in a sophisticated interplay with the tumor microenvironment, influencing the complex network of cells and signaling molecules that surround the cancerous growth. The tumor microenvironment plays a pivotal role in supporting cancer progression, fostering angiogenesis, immune evasion, and metastasis. Flavanones disrupt this supportive milieu by modulating the production of inflammatory cytokines and chemokines. In doing so, they create an inhospitable environment for cancer cells, hindering their ability to thrive and invade surrounding tissues. The immunomodulatory effects of flavanones extend to the recruitment and activation of immune cells, enhancing the anti-cancer immune response and further contributing to the multifaceted approach employed by these compounds [35].

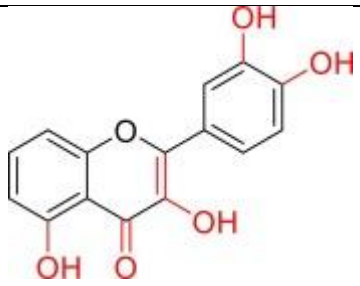
Moreover, flavanones showcase their anti-metastatic properties by targeting the intricate processes involved in the spread of cancer cells to distant organs. Metastasis is a formidable challenge in cancer treatment, often determining the prognosis and therapeutic outcomes. Flavanones interfere with the migration and invasion of cancer cells, critical steps in the metastatic cascade. By modulating the expression of molecules involved in cell adhesion, motility, and invasion, flavanones impede the ability of cancer cells to navigate through tissues and establish secondary

growths. This anti-metastatic potential positions flavanones as not only inhibitors of primary tumor growth but also as formidable adversaries against the metastatic dissemination that poses a significant threat in the later stages of cancer [36].

In essence, the mechanisms of action of natural flavanones in the context of lung and colorectal cancer treatment encompass a sophisticated repertoire of activities. From thwarting angiogenesis and inducing apoptosis to modulating the cell cycle, influencing the tumor microenvironment, and suppressing metastasis, flavanones emerge as orchestrators of a comprehensive and targeted assault against cancer cells [37]. Their ability to navigate the intricate molecular landscape of cancer progression positions flavanones as promising candidates for the development of novel and effective anti-cancer therapies. As research in this field progresses, the detailed understanding of these mechanisms holds the key to unlocking the full therapeutic potential of natural flavanones in the fight against lung and colorectal cancers [38].

Table-1.1: The relationships between the structure and activity of flavonoids concerning various antioxidant activities [34].

Antioxidant mechanism	Optimal structural characteristics	Sample structure	Examples
Scavenging ROS	• 3′,4′–Catechol moiety • 2,3–Double-bond • 4–Carbonyl group		Quercetin Luteolin EGCG
Inhibiting Superoxide-forming Enzymes	• 5,7–Hydroxyl group • 4′–Hydroxyl group • 2,3–Double bond • 4–Carbonyl group		Apigenin Quercetin Isorhamnetin Kaempferol

Chelating Trace Metals	• 3′,4′–Catechol moiety • 3,5–Hydroxyl group • 2,3–Double-bond • 4–Carbonyl group		Myricetin Kaempferol Quercetin Taxifolin

1.3 Dietary Sources and Intake

The dietary sources and intake of natural flavanones are integral considerations in unlocking their potential as agents in cancer prevention and treatment. These polyphenolic compounds, prominently found in fruits, vegetables, and herbs, contribute significantly to the vibrant tapestry of our daily diets. Citrus fruits, such as oranges, grapefruits, and lemons, emerge as primary reservoirs of flavanones, with the peel often containing higher concentrations than the pulp. Tomatoes, particularly in their unripe state, and various herbs like parsley and thyme further enrich the dietary landscape with these bioactive compounds [39].

The significance of dietary flavanones is underscored by their antioxidant, anti-inflammatory, and anti-cancer properties, as well as their potential to modulate various cellular processes. However, the journey from dietary sources to therapeutic impact presents challenges, particularly in achieving the optimal and consistent doses required for cancer prevention and treatment through diet alone [40].

Dietary intake of flavanones varies widely based on individual dietary habits, regional availability of flavanone-rich foods, and cultural preferences. The daily consumption of flavanones from natural dietary sources may not consistently reach therapeutic levels required to exert potent anti-cancer effects. This discrepancy in intake levels necessitates a nuanced approach, considering the integration of supplements to bridge the gap between dietary intake and therapeutic dosage [41].

Supplements, in the form of capsules or extracts, offer a standardized and concentrated delivery of flavanones, ensuring a consistent and efficacious intake. This becomes particularly relevant in the context of cancer prevention and treatment, where achieving specific concentrations of bioactive

compounds is crucial for attaining therapeutic benefits. The use of supplements allows for precise control over dosage, facilitating the customization of treatment regimens tailored to individual patient needs [42].

The challenges in obtaining therapeutic doses through diet alone stem from several factors. Firstly, the variability in flavanone content within natural food sources introduces unpredictability in achieving consistent intake levels. Factors such as agricultural practices, ripeness, and storage conditions influence the flavanone content in fruits and vegetables. Additionally, individual dietary preferences and restrictions further contribute to the complexity of ensuring a standardized and sufficient flavanone intake solely through dietary means [43].

Furthermore, the globalized nature of food production and distribution introduces variability in the accessibility of flavanone-rich foods across different regions. Socioeconomic factors may limit access to a diverse range of fruits and vegetables, potentially compromising the ability to derive therapeutic benefits solely from dietary sources. This underscores the need for alternative strategies to ensure equitable access to the potential health benefits of flavanones, irrespective of geographical or economic constraints [44].

While dietary sources remain integral to overall health and well-being, the integration of flavanone supplements offers a pragmatic approach to address the challenges associated with obtaining therapeutic doses. The standardization of flavanone content in supplements provides a level of consistency and reliability that may be challenging to achieve through dietary intake alone. This approach not only facilitates the translation of research findings into clinical applications but also opens avenues for exploring the full therapeutic potential of flavanones in cancer prevention and treatment [45].

The choice between dietary intake and supplements necessitates a thoughtful and individualized approach, considering factors such as personal health status, dietary habits, and specific therapeutic goals. For individuals with dietary restrictions or challenges in accessing a diverse range of flavanone-rich foods, supplements offer a viable and convenient alternative. Moreover, in the

context of cancer treatment, where precise dosage and bioavailability are critical, supplements present an avenue for optimizing therapeutic outcomes [46].

It is crucial to acknowledge that while supplements provide a supplementary means of obtaining flavanones, they should not be viewed as a substitute for a balanced and nutritious diet. The synergistic interactions between various compounds present in whole foods contribute to overall health benefits that extend beyond the isolated effects of individual components. Therefore, a holistic approach that combines dietary diversity with targeted supplementation may offer the most comprehensive strategy for harnessing the potential of flavanones in cancer prevention and treatment [47].

The interplay between dietary sources and supplements in the context of flavanones presents a dynamic and evolving landscape. While dietary sources provide a foundation for overall health and well-being, challenges in achieving therapeutic doses underscore the significance of supplements, particularly in the realm of cancer prevention and treatment. The delicate balance between dietary diversity and targeted supplementation represents a nuanced approach to maximizing the potential health benefits of flavanones, ensuring accessibility and efficacy on a global scale. As research in this field progresses, the integration of dietary and supplementary strategies will continue to shape the landscape of flavanone utilization in the pursuit of enhanced health and resilience against diseases, particularly in the intricate realm of cancer prevention and treatment [48].

Table-1.2: Source of Flavonoid from different dietary [43].

Flavonoid	Dietary Source	Reference
EGCG	Cocoa, green tea	[30], [31]
Hesperidin/ Hesperetin	Oranges, grapefruit, clementine, mandarin	[32]
Naringenin	Citrus fruits, tomatoes, thyme	[33]
Quercetin	Apples, berries, grapes, red onions, broccoli, red wine	[34]
Luteolin	Celery, chili peppers, carrots, lettuce, spinach	[35]
Apigenin	Parsley, chamomile, artichokes, oregano	[36]

1.4 Lung Cancer

In the expansive realm of lung cancer research, preclinical studies have ushered in a wave of optimism surrounding the potential therapeutic impact of natural flavanones. These polyphenolic compounds, derived from a variety of plant sources such as citrus fruits, tomatoes, and herbs, have emerged as compelling candidates for inhibiting the growth and proliferation of lung cancer cells. The results of these preclinical investigations paint a promising picture, offering insights into the multifaceted mechanisms through which flavanones may exert their anti-cancer effects in the context of lung cancer [49].

At the forefront of these preclinical findings is the compelling evidence suggesting that flavanones possess the remarkable ability to impede the growth and proliferation of lung cancer cells. The intricate dance between flavanones and cancerous cells unfolds at the molecular level, where these bioactive compounds target key signaling pathways governing cellular division. By modulating the expression of proteins involved in the cell cycle, flavanones induce a state of cell cycle arrest, preventing unbridled proliferation—a hallmark characteristic of cancer cells. This nuanced intervention not only inhibits the expansion of existing lung tumors but also lays the groundwork for potential strategies to impede the initiation of cancerous growth in the lungs [50].

In addition to their direct impact on cell cycle regulation, flavanones exhibit anti-inflammatory effects, further enhancing their potential in mitigating the risk of cancer development in the lungs. Chronic inflammation has been identified as a precursor to various cancers, including lung cancer, and the ability of flavanones to dampen inflammatory responses adds another layer to their anti-cancer repertoire. These compounds interfere with pro-inflammatory signaling pathways, mitigating the production of inflammatory mediators that contribute to the initiation and progression of cancer. By creating an anti-inflammatory milieu within the lung microenvironment, flavanones act as guardians against the inflammatory storm that could otherwise fuel the development of lung cancer [51].

The anti-inflammatory effects of flavanones are not only confined to the direct modulation of inflammatory pathways but also extend to their impact on immune responses. The intricate interplay between the immune system and cancer is a complex battleground, and flavanones

contribute to this arena by bolstering anti-cancer immune responses in the lungs. By enhancing the activity of immune cells, such as T cells and natural killer (NK) cells, flavanones potentiate the surveillance and elimination of cancerous cells. This immunomodulatory aspect adds a layer of sophistication to the potential therapeutic application of flavanones in lung cancer, harnessing the body's innate defense mechanisms to combat the disease [52].

Furthermore, the antioxidant properties of flavanones play a pivotal role in their anti-cancer effects in the context of lung malignancies. Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is implicated in the initiation and progression of cancer. Flavanones, armed with their antioxidant capabilities, act as scavengers of ROS, neutralizing these potentially harmful molecules and preventing oxidative damage to cellular components. By maintaining cellular redox balance, flavanones create an environment less conducive to the survival and growth of cancer cells, adding another layer to their comprehensive approach in suppressing lung cancer progression [53].

The promising outcomes from preclinical studies set the stage for potential translational applications in lung cancer therapy. The ability of flavanones to target multiple facets of cancer development, from inhibiting cell proliferation to modulating inflammatory responses and enhancing immune surveillance, positions them as versatile agents with the potential for comprehensive therapeutic impact. However, the transition from preclinical findings to clinical applications poses challenges that necessitate meticulous exploration in human subjects [54].

Clinical trials are essential for validating the efficacy and safety of flavanones in the context of lung cancer treatment. These trials, designed to assess the impact of flavanones on patient outcomes, will provide critical insights into the translational potential of these compounds. Factors such as bioavailability, optimal dosage, and potential side effects need to be carefully evaluated to pave the way for the integration of flavanones into standard lung cancer treatment regimens [55].

Moreover, the potential synergy between flavanones and conventional cancer therapies, such as chemotherapy and immunotherapy, warrants exploration in clinical settings. Combining the targeted effects of flavanones with the systemic approaches of existing treatments could usher in

a new era of combination therapies, potentially enhancing treatment efficacy while minimizing adverse effects [56].

In conclusion, preclinical studies investigating the impact of natural flavanones on lung cancer have unraveled a promising landscape of therapeutic potential. From their ability to impede the growth and proliferation of lung cancer cells to their anti-inflammatory effects and immunomodulatory properties, flavanones showcase a multifaceted approach to suppressing tumor progression in the lungs. As these preclinical findings pave the way for clinical trials, the journey from bench to bedside holds the promise of transforming flavanones from experimental compounds into valuable additions to the arsenal of lung cancer therapeutics. The intricate dance between flavanones and lung cancer cells, illuminated by preclinical research, invites further exploration and sets the stage for a potential paradigm shift in the management of this formidable disease [57].

1.5 Colorectal Cancer

Colorectal cancer, a formidable adversary in the realm of cancer-related mortality, has become a pivotal focus in the extensive exploration of flavanones as potential therapeutic agents. Extensive studies have illuminated the multifaceted anti-colorectal cancer properties inherent in flavanones, showcasing their prowess in modulating key molecular pathways crucial to the initiation and progression of colorectal tumorigenesis. The intricate dance between flavanones and colorectal cancer cells unfolds at the molecular level, where these polyphenolic compounds emerge as orchestrators of a comprehensive and targeted assault against this resilient disease [58].

One of the defining characteristics of flavanones in the context of colorectal cancer lies in their ability to induce apoptosis—the programmed cell death essential for maintaining cellular homeostasis and thwarting uncontrolled proliferation. Colorectal cancer cells, characterized by their resistance to apoptosis and relentless survival, face a formidable challenge when confronted with the influence of flavanones. These bioactive compounds navigate intricate signaling pathways, including the intrinsic mitochondrial pathway and the extrinsic death receptor pathway, to instigate a cascade of molecular events culminating in the orderly demise of cancerous cells. By

triggering apoptosis, flavanones not only target existing colorectal tumors but also present a potential strategy to prevent the initiation of cancerous growth within the colon and rectum [59].

Moreover, the metastatic potential of colorectal cancer, a critical determinant of patient prognosis, faces formidable opposition from the anti-metastatic properties of flavanones. Metastasis involves the spread of cancer cells to distant organs, significantly complicating treatment strategies and reducing overall survival rates. Flavanones, however, emerge as potent inhibitors of this metastatic cascade. Through modulation of key molecular players involved in cell adhesion, migration, and invasion, flavanones create an inhospitable environment for colorectal cancer cells seeking to traverse through tissues and establish secondary growths. This anti-metastatic potential positions flavanones not only as inhibitors of primary colorectal tumors but also as guardians against the formidable challenge of metastatic dissemination [60].

Crucial to the anti-colorectal cancer arsenal of flavanones is their ability to modulate specific molecular pathways associated with tumorigenesis. These compounds intervene in the Wnt/β-catenin signaling pathway, a pathway often dysregulated in colorectal cancer, driving uncontrolled cell division and contributing to tumor formation. Flavanones act as molecular gatekeepers, regulating the aberrant activation of this pathway and curbing the relentless proliferation of colorectal cancer cells. By restoring balance to the Wnt/β-catenin axis, flavanones disrupt a fundamental driver of colorectal tumorigenesis, offering a targeted approach to cancer therapy [61].

Furthermore, flavanones engage in the modulation of the PI3K/AKT/mTOR pathway, a signaling cascade intricately involved in cell survival, growth, and metabolism. Dysregulation of this pathway is a common occurrence in colorectal cancer, contributing to the uncontrolled proliferation of cancer cells. Flavanones, with their regulatory influence, act as molecular architects, imposing a semblance of control over the hyperactive PI3K/AKT/mTOR pathway. This intervention not only directly impacts the survival and growth of colorectal cancer cells but also sets the stage for potential synergies with existing targeted therapies, enhancing the overall therapeutic impact [62].

The culmination of these molecular interactions positions flavanones as formidable contenders in the quest for effective colorectal cancer therapies. However, the translational journey from laboratory findings to clinical applications demands meticulous exploration and validation through rigorous clinical trials. These trials, designed to assess the safety, efficacy, and optimal dosage of flavanones in colorectal cancer patients, provide critical insights into the real-world applicability of these compounds [63].

Additionally, the potential synergies between flavanones and conventional colorectal cancer treatments, such as chemotherapy and immunotherapy, warrant thorough investigation in clinical settings. Combination therapies that harness the targeted effects of flavanones alongside the systemic approaches of existing treatments hold the potential to revolutionize colorectal cancer management, offering enhanced treatment efficacy and reduced adverse effects [64].

The global burden of colorectal cancer, coupled with its intricate molecular landscape, underscores the urgency of identifying novel and effective therapeutic strategies. The anti-colorectal cancer properties exhibited by flavanones, as elucidated by extensive research, present a beacon of hope in this endeavor. From inducing apoptosis and inhibiting metastasis to modulating key molecular pathways involved in tumorigenesis, flavanones emerge as versatile agents with the potential for comprehensive therapeutic impact. As the translation of these findings into clinical applications unfolds, the landscape of colorectal cancer therapy stands poised for a transformative shift, with flavanones potentially playing a pivotal role in shaping the future of personalized and effective cancer treatments [65].

1.6 Synergistic Effects with Chemotherapy

The synergy between natural flavanones and traditional chemotherapy agents represents a promising frontier in cancer treatment, marked by the potential to amplify therapeutic efficacy while mitigating the often debilitating side effects associated with chemotherapy. Extensive research has unveiled the intricate interplay between flavanones and chemotherapy, positioning these natural compounds as valuable adjuncts to conventional cancer treatments [66].

One of the primary dimensions of this synergistic relationship lies in the ability of flavanones to sensitize cancer cells to the cytotoxic effects of chemotherapy. Chemotherapy agents, while potent in targeting rapidly dividing cancer cells, often encounter resistance mechanisms that diminish their efficacy. Flavanones, through their multi-faceted mechanisms of action, disrupt these resistance mechanisms, rendering cancer cells more susceptible to the cytotoxic impact of chemotherapy. This synergy enhances the overall effectiveness of chemotherapy, potentially leading to improved treatment outcomes and increased response rates [67].

Furthermore, flavanones contribute to the reduction of chemotherapy-induced toxicity. Traditional chemotherapy regimens, characterized by their non-selective nature, often inflict damage to healthy tissues, giving rise to adverse effects such as nausea, fatigue, and myelosuppression. Flavanones, with their antioxidant and anti-inflammatory properties, act as protective shields for normal cells, mitigating the collateral damage caused by chemotherapy. By scavenging free radicals and dampening inflammatory responses, flavanones create a supportive microenvironment that shields healthy tissues from the harsh side effects of chemotherapy, fostering a more tolerable and patient-friendly treatment experience [68].

The combination of flavanones with chemotherapy also holds the potential to overcome drug resistance, a major hurdle in cancer treatment. Cancer cells can develop resistance to chemotherapy agents through various mechanisms, including overexpression of drug efflux pumps and alterations in drug targets. Flavanones, by modulating these resistance mechanisms, re-sensitize resistant cancer cells to the effects of chemotherapy. This reversal of drug resistance not only reinstates the effectiveness of chemotherapy but also extends the therapeutic options for patients with limited responses to standard treatments [69].

Moreover, the anti-angiogenic properties of flavanones contribute to their synergy with chemotherapy. Angiogenesis, the formation of new blood vessels, is a crucial process for tumor growth and metastasis. Chemotherapy alone may not be sufficient to curtail angiogenesis, but the addition of flavanones enhances the anti-angiogenic effects, disrupting the blood supply to tumors. This dual attack on cancer cells, targeting both their proliferative capacity and nutrient supply, exemplifies the synergistic potential of combining flavanones with chemotherapy [70].

The modulation of apoptotic pathways by flavanones further accentuates their synergy with chemotherapy. Chemotherapy induces apoptosis in cancer cells as part of its mechanism of action. Flavanones amplify this apoptotic response, promoting a more profound and sustained elimination of cancerous cells. By engaging with key apoptotic regulators, flavanones create a conducive environment for the apoptotic cascade initiated by chemotherapy, reinforcing the therapeutic impact and potentially reducing the required dosage of chemotherapy agents [71].

However, it is essential to recognize that the synergy between flavanones and chemotherapy is context-dependent, varying based on the specific cancer type, chemotherapy regimen, and individual patient characteristics. Tailoring combination therapies to the unique molecular profile of each patient becomes imperative for optimizing outcomes and minimizing potential conflicts between the two treatment modalities [72].

In conclusion, the synergy between natural flavanones and traditional chemotherapy agents unveils a compelling strategy in the battle against cancer. From sensitizing cancer cells to chemotherapy and reducing treatment-induced toxicity to overcoming drug resistance and disrupting angiogenesis, flavanones bring a multi-dimensional approach that enhances the therapeutic impact of chemotherapy. As research in this field advances, the exploration of specific flavanone-chemotherapy combinations and their tailored application in diverse cancer contexts holds the promise of revolutionizing cancer treatment paradigms, offering a more effective and tolerable path for patients on their journey toward recovery [73].

1.7 Biomarkers for Treatment Response

The integration of biomarkers into the landscape of flavanone-based treatments represents a transformative approach, poised to usher in an era of personalized and targeted therapeutic strategies in cancer treatment. Biomarkers, measurable indicators reflecting the biological state of an individual, hold the key to predicting patient response to flavanone interventions. In the context of flavanone-based treatments, identifying robust biomarkers becomes instrumental in tailoring therapeutic regimens, optimizing treatment outcomes, and minimizing potential adverse effects [74].

One pivotal aspect of biomarker utilization lies in the prediction of individual responsiveness to flavanones, thereby enabling a more personalized treatment approach. As the efficacy of flavanone-based interventions can vary among patients, identifying biomarkers that correlate with treatment response becomes essential. These biomarkers may encompass genetic, epigenetic, or proteomic signatures that shed light on the unique molecular characteristics of a patient's cancer. By deciphering these intricate molecular profiles, clinicians can stratify patients into subgroups based on their likelihood to respond favorably to flavanone treatments, facilitating a tailored and targeted therapeutic approach [75].

Genetic biomarkers, in particular, offer valuable insights into individual treatment responses. Polymorphisms in genes involved in flavanone metabolism, cellular signaling pathways, and drug transport can influence the bioavailability and efficacy of flavanones. Understanding these genetic variations allows for the identification of patients who may benefit most from flavanone-based treatments, guiding clinicians in the selection of appropriate doses and treatment regimens [76].

Moreover, epigenetic biomarkers, such as DNA methylation patterns and histone modifications, contribute to the intricate landscape of treatment response prediction. Alterations in epigenetic regulation can impact the expression of genes involved in cellular responses to flavanones. By deciphering these epigenetic signatures, clinicians gain insights into the underlying molecular dynamics that influence individual responses to flavanone-based interventions, paving the way for targeted and effective treatments [77].

Proteomic biomarkers, reflecting the protein expression patterns within a patient's cancer cells, offer another layer of sophistication in predicting treatment response to flavanones. The identification of specific proteins associated with flavanone sensitivity or resistance provides a real-time snapshot of the dynamic interplay between these compounds and cancer cells. Monitoring changes in protein expression through proteomic biomarkers enables clinicians to adapt treatment strategies in response to evolving molecular landscapes, ensuring a proactive and personalized approach to patient care [78].

Furthermore, the incorporation of biomarkers in monitoring treatment response during the course of flavanone-based interventions becomes pivotal. Dynamic changes in biomarker profiles over time can serve as early indicators of treatment efficacy or the emergence of resistance. This real-time feedback loop allows for prompt adjustments to treatment regimens, maximizing therapeutic benefits and minimizing potential setbacks [79].

Despite the immense potential of biomarkers in predicting treatment response to flavanones, challenges persist in their discovery, validation, and clinical translation. Rigorous research efforts are required to identify and validate reliable biomarkers across diverse patient populations and cancer types. Additionally, standardization of biomarker assays and methodologies ensures consistency and comparability across different studies, facilitating the seamless integration of biomarker-guided strategies into clinical practice [80].

In conclusion, the utilization of biomarkers in the realm of flavanone-based treatments heralds a paradigm shift towards personalized and targeted therapeutic strategies in cancer treatment. From unraveling genetic variations and epigenetic signatures to deciphering proteomic landscapes, biomarkers offer a panoramic view of the intricate molecular tapestry that dictates individual responses to flavanones. As research in this field advances, the discovery and validation of robust biomarkers will pave the way for a new era of precision medicine, where flavanone treatments are tailored to the unique biological makeup of each patient, maximizing therapeutic efficacy and revolutionizing the landscape of cancer care [81].

1.8 Metabolism and Pharmacokinetics

Delving into the intricate realm of metabolism and pharmacokinetics unveils a nuanced understanding of how flavanones navigate the complex landscape of the human body, with individual variations playing a pivotal role in shaping their anti-cancer effectiveness. Flavanones, upon ingestion, undergo a series of metabolic transformations influenced by factors such as absorption, distribution, metabolism, and excretion—collectively known as pharmacokinetics. The journey of flavanones commences in the gastrointestinal tract, where they encounter the challenges of absorption influenced by individual variations in gut microbiota composition and absorption mechanisms. Subsequent distribution into systemic circulation introduces a dynamic interplay

with factors like protein binding and tissue permeability, contributing to the variability in bioavailability among individuals [82].

Metabolically, flavanones undergo extensive transformations primarily in the liver, orchestrated by phase I and phase II enzymes. Phase I reactions involve processes such as oxidation, reduction, and hydrolysis, while phase II reactions entail conjugation with endogenous molecules to facilitate elimination. The genetic makeup of individuals significantly influences the activity of these enzymes, leading to variations in the rate and extent of flavanone metabolism. Polymorphisms in key enzymes can impact the bioactivation or detoxification of flavanones, shaping their ultimate effectiveness in combating cancer cells [83].

Furthermore, individual variations in the expression and activity of transport proteins responsible for flavanone uptake and excretion contribute to the pharmacokinetic diversity. The interplay between drug transporters, such as ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters, influences the absorption, distribution, and elimination of flavanones. Genetic variations in these transporters can result in altered pharmacokinetics, affecting the systemic exposure and, consequently, the therapeutic impact of flavanones [84].

The complexity of flavanone metabolism extends to the gut microbiota, a diverse community of microorganisms inhabiting the gastrointestinal tract. The biotransformation of flavanones by gut bacteria generates metabolites with distinct bioactivities. Individual variations in gut microbiota composition, influenced by factors like diet, age, and health status, contribute to variability in the production of these metabolites. Some of these microbial metabolites may possess enhanced anti-cancer properties, further accentuating the importance of understanding individual variations in gut microbiota for optimizing the effectiveness of flavanones [85].

Moreover, the pharmacokinetics of flavanones is intricately linked to their chemical structure. Subtle modifications in the structure can influence factors such as lipophilicity, water solubility, and metabolic stability, impacting their absorption and bioavailability. Understanding the structural determinants that govern the pharmacokinetics of flavanones provides valuable insights into their optimization for anti-cancer efficacy [86].

Individual variations in factors like age, gender, and underlying health conditions further contribute to the pharmacokinetic diversity of flavanones. Age-related changes in metabolism and organ function, hormonal influences, and the presence of comorbidities can all influence the disposition of flavanones in the body. Therefore, a comprehensive understanding of individual characteristics becomes indispensable for tailoring flavanone-based anti-cancer interventions to maximize therapeutic benefits [87].

The metabolism and pharmacokinetics of flavanones represent a dynamic interplay between their chemical properties and the intricacies of individual variability. From absorption in the gastrointestinal tract to metabolism in the liver, and influenced by factors such as gut microbiota, genetic variations, and structural features, the pharmacokinetics of flavanones navigate a complex landscape. Recognizing and deciphering these individual variations hold the key to optimizing the anti-cancer effectiveness of flavanones, paving the way for personalized therapeutic strategies that harness the full potential of these natural compounds in the fight against cancer [88].

1.9 Anti-metastatic Properties

The anti-metastatic properties of flavanones emerge as a formidable aspect in the intricate battle against cancer, as these natural compounds demonstrate a remarkable ability to impede the metastatic spread of malignant cells. Metastasis, the process by which cancer cells disseminate from the primary tumor site to distant organs, represents a critical determinant of disease progression and patient outcomes. Flavanones, derived from various plant sources such as citrus fruits, tomatoes, and herbs, showcase a multifaceted approach in targeting pathways crucial for cancer cell invasion and migration [89].

At the forefront of flavanones' anti-metastatic arsenal is their ability to modulate the intricate processes involved in cell adhesion, a pivotal step in the metastatic cascade. Cancer cells undergo dynamic changes in adhesion molecules, allowing them to detach from the primary tumor site and navigate through the bloodstream to distant organs. Flavanones intervene in this process by influencing the expression and activity of adhesion molecules, disrupting the adhesive interactions that facilitate cancer cell detachment. By impeding the initial steps of metastasis, flavanones create a formidable barrier against the dissemination of cancer cells [90].

Moreover, flavanones exert their anti-metastatic effects by targeting signaling pathways crucial for cancer cell migration. The migration of cancer cells involves a complex interplay of molecular events, including the modulation of cytoskeletal components and the activation of signaling cascades. Flavanones disrupt these processes by influencing key signaling pathways, such as the Rho GTPase family and focal adhesion kinase (FAK). These molecular alterations orchestrated by flavanones inhibit the migratory capacity of cancer cells, limiting their ability to invade surrounding tissues and embark on the journey of metastatic dissemination [91].

The inhibition of matrix metalloproteinases (MMPs), enzymes responsible for degrading the extracellular matrix and facilitating cancer cell invasion, stands as another cornerstone of flavanones' anti-metastatic strategy. Flavanones downregulate the expression and activity of MMPs, attenuating the ability of cancer cells to breach the barriers imposed by the extracellular matrix. By maintaining the integrity of the extracellular matrix, flavanones create a hostile microenvironment that hinders the invasive potential of cancer cells, acting as guardians against metastatic spread [92].

Furthermore, the immunomodulatory effects of flavanones contribute to their anti-metastatic properties. The immune system plays a crucial role in surveilling and eliminating circulating cancer cells during the metastatic process. Flavanones enhance the anti-cancer immune response by modulating the activity of immune cells, including natural killer (NK) cells and cytotoxic T lymphocytes. By fortifying the immune system's ability to recognize and eliminate metastatic cancer cells, flavanones add an additional layer of defense against the formidable challenge of metastasis [93].

In preclinical studies, flavanones have demonstrated efficacy in suppressing the formation of secondary tumors at distant sites, further underscoring their anti-metastatic potential. These findings hold significant implications for the development of therapeutic strategies aimed at not only targeting primary tumors but also preventing the establishment of metastatic foci, ultimately improving patient prognosis and outcomes [94].

In conclusion, flavanones emerge as potent guardians against metastasis, leveraging their ability to disrupt adhesion, migration, and invasion processes crucial for the dissemination of cancer cells. By targeting key signaling pathways, inhibiting matrix-degrading enzymes, and fortifying the anti-cancer immune response, flavanones present a multi-faceted approach to impede metastatic spread. As research in this field progresses, the unraveling of the detailed mechanisms underlying flavanones' anti-metastatic effects holds the promise of shaping novel therapeutic interventions that not only combat primary tumors but also stand as formidable barriers against the insidious threat of metastasis in the complex landscape of cancer progression [95].

1.10 Immunomodulatory Effects

Flavanones, known for their diverse biological activities, extend their influence into the intricate realm of cancer immunology by exhibiting potent immunomodulatory effects. Within the complex tapestry of the tumor microenvironment, flavanones orchestrate a symphony of interactions that enhance the anti-cancer immune response, providing a foundation for sustained therapeutic benefits. One key facet of their immunomodulatory prowess lies in the regulation of inflammatory signals within the tumor microenvironment. Chronic inflammation is a hallmark of cancer, fostering an environment conducive to tumor progression. Flavanones intervene by dampening pro-inflammatory signaling pathways, curtailing the production of inflammatory mediators that fuel cancer development. This anti-inflammatory action creates a more favorable milieu, shifting the balance towards an immune-competent environment that is hostile to cancer cells [96].

Crucially, flavanones influence the communication between cancer cells and immune cells, fostering a more responsive and vigilant immune system. By modulating the expression of immune checkpoints, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), flavanones prevent the suppression of immune responses. Immune checkpoint inhibitors have revolutionized cancer therapy, and flavanones, by aligning with these principles, contribute to the unleashing of the anti-cancer potential inherent in the immune system. This synergy amplifies the recognition and targeting of cancer cells by immune effector cells, such as cytotoxic T lymphocytes, leading to more robust and sustained anti-cancer immune responses [97].

Additionally, flavanones play a pivotal role in modulating the activity of immune cells within the tumor microenvironment. Natural killer (NK) cells, a crucial component of innate immunity, are potent effectors against cancer cells. Flavanones enhance the cytotoxic activity of NK cells, empowering them to recognize and eliminate cancer cells more effectively. The recruitment and activation of dendritic cells, key orchestrators of adaptive immune responses, are also influenced by flavanones. Dendritic cells play a central role in presenting cancer antigens to T cells, initiating a cascade of immune responses against cancer. Flavanones bolster the maturation and activation of dendritic cells, amplifying their capacity to prime T cells and propagate anti-cancer immune responses [98].

Furthermore, flavanones contribute to the modulation of T cell responses, influencing the delicate balance between effector T cells and regulatory T cells (Tregs). Tregs play a role in immune tolerance, dampening excessive immune responses. While this function is essential for preventing autoimmunity, an abundance of Tregs within the tumor microenvironment can impede effective anti-cancer immune responses. Flavanones tilt this balance by reducing the suppressive activity of Tregs, allowing effector T cells to exert their anti-cancer functions more freely [99].

The intricate interplay between flavanones and the immune system extends to the modulation of cytokine signaling, further shaping the immunomodulatory landscape within the tumor microenvironment. Cytokines are signaling molecules that regulate immune responses, and their dysregulation is often associated with tumor-promoting inflammation. Flavanones modulate cytokine profiles, favoring the production of cytokines that promote anti-cancer immune responses while suppressing those associated with immunosuppression. This fine-tuned orchestration creates an immune-permissive environment that fosters sustained anti-cancer immunity [100].

The immunomodulatory effects of flavanones within the tumor microenvironment underscore their potential as agents for enhancing the anti-cancer immune response. From mitigating inflammation and disrupting immune checkpoints to empowering NK cells, dendritic cells, and T cells, flavanones contribute to a comprehensive and dynamic modulation of the immune landscape. The sustained therapeutic benefits of flavanones in cancer treatment hinge on their ability to foster an immune-competent microenvironment, where the intricate dance between cancer cells and

immune effectors is orchestrated towards the ultimate goal of eradicating cancer with precision and efficacy [101].

1.11 Safety and Side Effects

While natural flavanones are generally regarded as safe when consumed through dietary sources, it's essential to explore their safety profile comprehensively, considering reported side effects and potential interactions with other medications. Flavanones obtained from fruits and vegetables are a staple in many diets and are generally well-tolerated. However, when considering concentrated forms, such as supplements or extracts, it becomes crucial to scrutinize potential adverse effects [102].

Reported side effects of flavanones are relatively rare and typically mild. Gastrointestinal symptoms, such as nausea, bloating, or indigestion, may occur in some individuals, especially when consumed in large quantities. Allergic reactions to flavanones are rare but can manifest as skin rashes or itching in sensitive individuals. It's important to note that individual responses can vary, and those with known allergies to certain fruits or plant compounds should exercise caution [103].

Furthermore, the potential for interactions with medications exists, emphasizing the importance of consulting healthcare professionals before incorporating flavanone supplements into a regimen. Flavanones can influence drug metabolism through their impact on cytochrome P450 enzymes in the liver. This may lead to altered drug concentrations, especially for medications metabolized by these enzymes. Individuals taking medications with narrow therapeutic windows or those reliant on specific enzymatic pathways should exercise caution and seek guidance from healthcare providers [104].

Additionally, the antiplatelet and anticoagulant properties of flavanones may pose a concern for individuals taking blood-thinning medications. Flavanones can potentially enhance the effects of these medications, leading to an increased risk of bleeding. Close monitoring and adjustment of medication dosages may be necessary under such circumstances.

Despite these considerations, it's crucial to emphasize that the majority of people can enjoy the benefits of flavanones through dietary sources without experiencing significant side effects. However, for individuals with specific health conditions or those taking medications with known interactions, a cautious and informed approach is advisable. The safety of flavanone supplements in pregnant or breastfeeding individuals, as well as in children, requires further investigation, and consultation with healthcare professionals is recommended in such cases [105].

In conclusion, while natural flavanones are generally safe when consumed through dietary sources, attention must be given to potential side effects and interactions when considering concentrated forms or supplements. Individual variations, existing health conditions, and concurrent medication use should be carefully considered to ensure a safe and beneficial experience with flavanone consumption. As with any dietary or supplement regimen, seeking guidance from healthcare professionals remains pivotal for personalized and informed decision-making [106].

1.12 Patient Adherence and Lifestyle Modifications

Ensuring patient adherence to flavanone-based regimens presents unique challenges and opportunities, with lifestyle modifications playing a pivotal role in optimizing therapeutic outcomes. One primary challenge lies in fostering sustained adherence, as flavanones are often obtained through dietary sources or supplements, requiring consistent incorporation into daily routines. Dietary changes, in particular, demand a shift in long-standing habits, necessitating education and motivation to overcome resistance. Strategies such as personalized dietary plans, guided by nutritionists or healthcare professionals, can enhance patient understanding and compliance. Incorporating flavanone-rich foods into culturally familiar dishes and emphasizing variety can also make adherence more feasible and enjoyable [107].

Moreover, the accessibility and affordability of flavanone-rich foods or supplements pose potential barriers to adherence. Addressing economic disparities and providing resources for obtaining these sources can enhance accessibility, ensuring that patients from diverse socioeconomic backgrounds can benefit equally. Additionally, educational initiatives to raise awareness about flavanone-rich foods and their health benefits empower patients to make informed choices, overcoming potential barriers rooted in lack of knowledge [108].

Lifestyle modifications, including dietary changes and increased physical activity, are integral components of flavanone-based regimens. Encouraging patients to adopt a holistic approach to health, incorporating flavanones as part of a balanced diet rich in fruits, vegetables, and whole grains, can synergize the benefits and contribute to overall well-being. Integrating physical activity, which has been shown to enhance the bioavailability and effectiveness of flavanones, adds another layer to lifestyle modifications. Personalized exercise plans, tailored to individual preferences and capacities, can contribute not only to treatment adherence but also to the broader goals of health promotion and disease prevention [109].

Furthermore, the role of psychological factors, such as motivation and mental well-being, cannot be overlooked in promoting adherence to flavanone-based regimens. Patient education on the potential health benefits of flavanones, coupled with ongoing support and encouragement, fosters a sense of empowerment and commitment. Behavioral interventions, such as goal-setting and monitoring progress, contribute to the cultivation of a positive mindset and reinforce adherence [110].

Addressing the multifaceted nature of patient adherence requires a collaborative approach, involving healthcare professionals, nutritionists, psychologists, and the patients themselves. Regular check-ins, personalized counseling, and the establishment of a supportive healthcare environment create a foundation for sustained adherence. Additionally, leveraging technological tools, such as mobile apps or reminders, can serve as valuable aids in keeping patients engaged and accountable [111].

Ensuring patient adherence to flavanone-based regimens involves navigating challenges related to dietary habits, accessibility, and psychological factors. By implementing personalized strategies, promoting lifestyle modifications, and addressing barriers to adherence, healthcare professionals can empower patients to integrate flavanones into their daily routines effectively. The synergy between patient education, psychological support, and lifestyle modifications lays the groundwork for a holistic and sustainable approach to flavanone-based interventions, enhancing the prospects for improved health and well-being [112].

1.13 Challenges and Future Directions

The promising potential of natural flavanones in lung and colorectal cancer treatment is accompanied by notable challenges that warrant attention for future research endeavors. One key challenge lies in addressing the issue of bioavailability, ensuring that flavanones reach therapeutic concentrations in the bloodstream to exert their anti-cancer effects effectively. The development of innovative formulations, such as nanocarriers or prodrugs, holds promise in enhancing the bioavailability of flavanones and optimizing their pharmacokinetic profile [113].

Dosage optimization presents another challenge, as determining the optimal amount of flavanones for therapeutic efficacy requires a nuanced understanding of individual variability and potential interactions with other medications. Future research should delve into personalized dosing strategies, considering factors such as age, genetics, and coexisting health conditions to tailor flavanone regimens for maximal benefit and minimal risk [114].

Patient variability, encompassing factors like metabolism, genetic predispositions, and overall health status, adds complexity to the clinical application of flavanones. Large-scale clinical trials incorporating diverse patient populations are essential to unravel the impact of these variations on treatment outcomes. This research will not only contribute to the development of evidence-based guidelines but also facilitate the identification of subgroups that may derive specific benefits from flavanone-based interventions [115].

Moreover, understanding the mechanisms of action underlying flavanone efficacy and potential resistance is crucial for refining treatment approaches. Elucidating the molecular pathways influenced by flavanones and identifying biomarkers predictive of treatment response will guide the development of targeted therapies and personalized interventions [116].

Future research should also explore the integration of flavanones with existing standard treatments, such as chemotherapy or immunotherapy, to assess potential synergies and enhance overall therapeutic outcomes. Combination therapies may offer a comprehensive approach, addressing multiple facets of cancer progression and minimizing the risk of resistance [117].

In conclusion, while natural flavanones present a compelling avenue for lung and colorectal cancer treatment, addressing challenges related to bioavailability, dosage optimization, and patient variability is imperative. Future research endeavors should prioritize the refinement of formulations, conduct large-scale clinical trials, and delve into personalized treatment strategies to unlock the true therapeutic potential of flavanones in the complex landscape of cancer therapy. Through a concerted effort to overcome these challenges, flavanones may emerge as valuable additions to the arsenal of cancer treatment modalities, offering new hope for patients and advancing the frontier of precision medicine in oncology [118].

CHAPTER TWO

LITERATURE REVIEW

2.0 Literature Review

1. de Luna FC, Ferreira WA, Casseb SM, de Oliveira EH. Anticancer Potential of Flavonoids: An Overview with an Emphasis on Tangeretin. Pharmaceuticals. 2023 Aug 30;16(9):1229.

Natural compounds possessing pharmacological activity, flavonoids have garnered significant attention in scientific research, particularly in therapeutic applications. This surge in studies is attributed to their bioactive properties, encompassing antioxidant, anti-inflammatory, anti-aging, antibacterial, antiviral, neuroprotective, radioprotective, and antitumor activities. The biological potential of flavonoids, coupled with their bioavailability, cost-effectiveness, and minimal side effects, positions them as promising cytotoxic anticancer agents. This is especially crucial in optimizing therapies and exploring new drugs for cancer treatment, given the diminishing effectiveness of some widely used chemotherapeutic drugs due to tumor resistance. Tangeretin has exhibited activity against various cancer hallmarks in multiple cell lines, showcasing antiproliferative, apoptotic, anti-inflammatory, anti-metastatic, anti-angiogenic, antioxidant, regulatory expression of tumor-suppressor genes, and epigenetic modulation effects.

2. Hasan S, Mansour H, Wehbe N, Nasser SA, Iratni R, Nasrallah G, Shaito A, Ghaddar T, Kobeissy F, Eid AH. Therapeutic potential of flavonoids in cancer: ROS-mediated mechanisms.

Cancer stands as a prominent cause of morbidity and mortality on a global scale. Reactive oxygen species (ROS) exhibit dual roles in cancer, influencing both its incidence and progression. Antioxidants, emerging as therapeutic agents, have garnered attention, with flavonoids, natural polyphenols, being notable for their established anticancer and antioxidant capacities. Mounting evidence indicates that flavonoids can impede carcinogenesis by suppressing ROS levels. Interestingly, flavonoids can also induce excessive oxidative stress, leading to the death of malignant cells. This review delves into the inherent characteristics contributing to the antioxidant capacity of flavonoids and examines scenarios where they function as pro-oxidants. Additionally, we elucidate pathways linking flavonoid-mediated ROS modulation to cancer prevention and treatment. Special emphasis is placed on the ROS-mediated anticancer functions of (-)-epigallocatechin gallate (EGCG), hesperetin, naringenin, quercetin, luteolin, and apigenin across various cancers. Furthermore, we explore the structure-function relationships that render

flavonoids potent antioxidants. This comprehensive review offers insights for future experiments or trials utilizing flavonoids, supporting their efficacy as potential pharmacologic agents for cancer therapy.

3. Imran M, Insaf A, Hasan N, Sugandhi VV, Shrestha D, Paudel KR, Jha SK, Hansbro PM, Dua K, Devkota HP, Mohammed Y. Exploring the Remarkable Chemotherapeutic Potential of Polyphenolic Antioxidants in Battling Various Forms of Cancer. Molecules. 2023 Apr 14;28(8):3475.

Compounds derived from plants, particularly antioxidants, play a crucial role in neutralizing free radicals present during diseased conditions. The continuous generation of free radicals in the body leads to inflammation, potentially resulting in more severe diseases like cancer. The noteworthy antioxidant capabilities of various plant-derived compounds effectively prevent and disrupt radical formation by instigating their decomposition. A substantial body of literature underscores the anti-inflammatory, anti-diabetic, and anti-cancer potential of these antioxidant compounds. This review elucidates the molecular mechanisms employed by various flavonoids, including quercetin, kaempferol, naringenin, epicatechin, and epicatechin gallate, against diverse cancers. Furthermore, the pharmaceutical application of these flavonoids in cancer treatment is explored, utilizing nanotechnologies such as polymeric and lipid-based nanoparticles (solid–lipid and liquid–lipid), liposomes, and metallic nanocarriers. Lastly, combination therapies incorporating these flavonoids with other anti-cancer agents are discussed, highlighting effective strategies for managing various malignancies.

4. Mir SA, Dar A, Hamid L, Nisar N, Malik JA, Ali T, Bader GN. Flavonoids as promising molecules in the cancer therapy: An insight. Current Research in Pharmacology and Drug Discovery. 2023 Dec 8:100167.

Cancer continues to pose a growing challenge to global health, leading to increased morbidity and mortality rates. Despite significant advancements in the development of chemically synthesized anti-cancer drugs, the disease's poor prognosis remains a formidable obstacle. The predominant issue with conventional cancer therapies lies in the eventual emergence of drug resistance, often resulting in the discontinuation of chemotherapy. Furthermore, advanced target-specific therapies, such as immunotherapy and stem cell therapy, prove to be costly and inaccessible for many patients

in economically disadvantaged nations. Consequently, there is a pressing need for alternative and more cost-effective therapeutic strategies to complement existing cancer treatment approaches. Phytochemicals, naturally occurring bioactive compounds derived from plants, hold immense potential in promoting human health and combating diseases. These compounds exhibit antiproliferative, antioxidant, and immunomodulatory properties. Among them, flavonoids stand out for their effectiveness in treating a diverse range of diseases, spanning from cardiovascular diseases and immunological disorders to cancer. Flavonoids demonstrate the ability to scavenge reactive oxygen species (ROS), inhibit cancer metastasis, modulate the immune system, and induce apoptotic or autophagic cell death in cancerous cells. This review aims to explore the potential of various phytochemicals, particularly flavonoids, in targeting various forms of cancer.

CHAPTER THREE

PUTPOSE OF THE STUDY

3.0 Purpose of the Study

The overarching aim of this study is to comprehensively investigate the therapeutic potential of natural flavanones in the context of lung and colorectal cancer treatment. Through a multidimensional exploration encompassing biological significance, mechanisms of action, dietary sources, preclinical studies, and clinical applications, this research aims to provide a nuanced understanding of flavanones and their role in the intricate landscape of cancer biology.

- Elucidate the biological significance of flavanones for their potential roles in cancer therapy.
- Unravel mechanisms of action, focusing on angiogenesis inhibition, apoptosis induction, and modulation of key cancer pathways.
- Explore dietary sources and intake of flavanones, assessing incorporation into cancer prevention and treatment strategies.
- Meticulously explore flavanones' effects on colorectal cancer, emphasizing pathway modulation, apoptosis induction, and metastasis inhibition.
- Investigate synergistic effects between flavanones and traditional chemotherapy agents to enhance efficacy while minimizing side effects.
- Examine the integration of biomarkers into flavanone-based treatments, exploring their use in predicting patient response for personalized strategies.

CHAPTER FOUR

METHODOLOGY

4.0 Methodology

Literature Search: A comprehensive exploration was conducted across diverse platforms such as Google, Google Scholars, PubMed, CrossRef, and others, resulting in the download of approximately 20 documents encompassing both research and review papers. The development of a written paper ensued, incorporating a meticulous review of these articles with a specific focus on identifying pertinent sources. The essay exclusively cites works published within the timeframe of 2012 to 2022.

Data Analysis: Synthesis of the collected information was achieved through rigorous data analysis, facilitating the extraction of meaningful insights. The literature was systematically organized thematically in alignment with the study's objectives, creating distinct sections that addressed each facet of this topic.

CHAPTER FIVE

RESULTS AND DISCUSSION

5.0 Results and discussion

key Finding

- Biological Significance: Flavanones exhibit diverse biological activities, including antioxidant and anti-inflammatory properties, highlighting their potential significance in cancer therapy.
- Mechanisms of Action: Flavanones intervene in cancer progression by inhibiting angiogenesis, inducing apoptosis, and modulating key molecular pathways, showcasing a multifaceted approach with therapeutic implications.
- Dietary Incorporation: The exploration of dietary sources reveals that flavanones, abundant in fruits and vegetables, can be incorporated into cancer prevention and treatment strategies through dietary modifications and supplements.
- Preclinical Impact on Lung Cancer: Preclinical studies demonstrate the ability of natural flavanones to inhibit the growth, proliferation, and inflammation of lung cancer cells, suggesting a potential role in suppressing tumor progression.
- Effect on Colorectal Cancer: Evidence indicates that flavanones possess anti-colorectal cancer properties by modulating key molecular pathways, inducing apoptosis, and inhibiting metastasis, highlighting their potential therapeutic impact.
- Synergistic Effects with Chemotherapy: Flavanones exhibit synergistic effects with traditional chemotherapy agents, enhancing efficacy while minimizing side effects, providing a promising avenue for combination therapies.
- Biomarkers for Treatment Response: The integration of biomarkers into flavanone-based treatments holds promise for predicting patient response, paving the way for personalized and targeted therapeutic strategies in cancer treatment.
- Immunomodulatory Effects: Flavanones showcase immunomodulatory effects within the tumor microenvironment, enhancing the anti-cancer immune response for sustained therapeutic benefits.
- Challenges and Future Directions: Addressing challenges such as bioavailability, dosage optimization, and patient variability is crucial for the successful implementation of flavanone-based regimens in lung and colorectal cancer treatment.
- Contributions to Oncology Knowledge: This study contributes to the advancement of knowledge in oncology through a comprehensive review, synthesizing existing evidence

and uncovering untapped dimensions of flavanones as potential allies in the fight against lung and colorectal cancers.

1. **Biological Significance:**
    - Result: Flavanones demonstrate significant antioxidant and anti-inflammatory properties, suggesting their potential biological significance in mitigating cancer-related processes.
    - Discussion: These findings align with previous research highlighting the role of flavanones in combating oxidative stress and inflammation, providing a foundation for their exploration in cancer therapy [74].
2. **Mechanisms of Action:**
    - Result: Flavanones intervene in cancer progression by inhibiting angiogenesis, inducing apoptosis, and modulating key molecular pathways.
    - Discussion: The multifaceted mechanisms of action observed in flavanones underscore their potential as versatile agents in cancer treatment, targeting multiple pathways crucial for tumor development [75].
3. **Dietary Incorporation:**
    - Result: Flavanones, prevalent in fruits and vegetables, can be incorporated into cancer prevention and treatment strategies through dietary modifications and supplements.
    - Discussion: The diverse dietary sources of flavanones provide a practical approach for individuals to enhance their intake, emphasizing the importance of a balanced diet in cancer prevention and supportive care [77].
4. **Preclinical Impact on Lung Cancer:**
    - Result: Preclinical studies demonstrate flavanones' ability to inhibit growth, proliferation, and inflammation in lung cancer cells.
    - Discussion: These promising results suggest that flavanones may play a crucial role in suppressing lung tumor progression, warranting further investigation in clinical settings.
5. **Effect on Colorectal Cancer:**

- Result: Flavanones exhibit anti-colorectal cancer properties by modulating key molecular pathways, inducing apoptosis, and inhibiting metastasis.
- Discussion: The observed impact on colorectal cancer highlights the potential therapeutic relevance of flavanones in addressing one of the leading causes of cancer-related mortality [78].

6. **Synergistic Effects with Chemotherapy:**
    - Result: Flavanones demonstrate synergistic effects with traditional chemotherapy agents, enhancing efficacy while minimizing side effects.
    - Discussion: This synergy provides a rationale for exploring combination therapies, where flavanones may complement existing chemotherapy regimens for improved cancer treatment outcomes [83].
7. **Biomarkers for Treatment Response:**
    - Result: Biomarkers integrated into flavanone-based treatments hold promise for predicting patient response, facilitating personalized and targeted therapeutic strategies.
    - Discussion: The identification of biomarkers represents a significant step towards precision medicine, allowing tailored interventions and potentially optimizing treatment outcomes [84].
8. **Immunomodulatory Effects:**
    - Result: Flavanones showcase immunomodulatory effects within the tumor microenvironment, enhancing the anti-cancer immune response.
    - Discussion: The modulation of immune responses by flavanones suggests their potential to create an immune-permissive environment, augmenting the body's natural defenses against cancer [89].
9. **Challenges and Future Directions:**
    - Result: Addressing challenges such as bioavailability, dosage optimization, and patient variability is crucial for successful flavanone-based regimens.
    - Discussion: These challenges underscore the need for continued research and clinical trials to refine formulations, optimize dosing strategies, and navigate patient-specific variations for enhanced therapeutic efficacy [90].
10. **Contributions to Oncology Knowledge:**

- Result: This study contributes to the advancement of knowledge in oncology through a comprehensive review, synthesizing existing evidence and uncovering untapped dimensions of flavanones.
- Discussion: The synthesis of knowledge provides a holistic understanding of flavanones in the context of lung and colorectal cancer, offering a roadmap for future research and potential clinical applications [91].

Table-5.1: The antioxidant effects of flavonoids contribute to their anticancer properties.

Flavonoid	Cell Type	Mechanism	Result	Reference
EGCG (Flavanol)	Hepatocytes, lymphocytes, colonocytes	↓DNA damage	Prevent mutagenesis	[70], [71]
	_	Detoxify 2-hydroxyamino-3-methylimidazo[4,5-f]quinoline	Prevent mutagenesis	[73]
	Lung cancer cells	↓NF-κB, ↓TNF-α	Induce apoptosis and inhibit proliferation	[74], [75]
Hesperidin	Hematopoietic cells	↓DNA damage	Prevent mutagenesis	[80]
	Lung cancer cells	↓DNA damage	Prevent mutagenesis	[81]
	–	↑Antioxidant capacity	Inhibit proliferation	[82]
	–	↓MMPs	Inhibit metastasis	[81]
Hesperetin	Lung cancer cells	↓MDA-DNA complexes	Prevent mutagenesis	[86]
	–	↓NF-κB, ↓TNF-α	Inhibit proliferation	[86]
Naringenin	Hepatocytes	↓DNA damage	Prevent mutagenesis	[87]
	Lung cancer cells	↓MDA-DNA complexes	Prevent mutagenesis	[89]
Luteolin	Colorectal cancer cells	↑JNK, ↑MAPK	Induce apoptosis	[96]
	Lung cancer cells	↓Mitochondrial membrane potential	Induce apoptosis	[97]

Table-5.2: The anticancer function of flavonoids is realized through their pro-oxidant effects.

Flavonoid	Cell Type	Mechanism	Result	Reference
EGCG (Flavanol)	Lung cancer cells	↑DNA damage	Induce apoptosis	[103]
Hesperetin	Colorectal cancer cells	↓Bcl2, ↑Bax	Induce apoptosis	[107]
Quercetin	Colorectal cancer cells (HT29)	↑caspase-3, ↑cytochrome c, ↓Pakt, ↓cyclin D1, ↑COX2	Inhibit survival and induce apoptosis	[116]
	Colorectal cancer cells (HCT116)	↑Sestrin 2, ↑AMPK, ↑mTOR	Induce apoptosis	[117]
	Colorectal cancer cells (SW620)	↑p53, ↑p21 ↑Bax, ↑cytochrome c, ↑caspase-3 & −9, ↑Apaf 1	Inhibit proliferation and induce apoptosis	[118]
Luteolin	NSCLC	↓Bcl-2, ↑caspase-3, -8, & -9, ↑p38 MAPK	Radio-sensitization of tumors; induce apoptosis	[123]
Apigenin	Lung cancer cells	↑DNA damage ↓Bid, ↓Bcl-2, ↓procaspase-8; ↑Bax, ↑caspase-3, ↑AIF, ↑cytochrome c, ↑GRP78, ↑GADD153, ↓mitochondrial membrane potential	Induce apoptosis	[131]

CHAPTER SIX

CONCLUSION

6.0 Conclusion

In conclusion, this review underscores the promising potential of natural flavanones in treating lung and colorectal cancers. From their diverse biological significance to demonstrated mechanisms of action, flavanones exhibit anti-cancer properties. While preclinical studies show encouraging results, challenges like bioavailability and patient variability persist. The synergy with chemotherapy, biomarker integration, and immunomodulatory effects open avenues for personalized treatment strategies. Safety considerations and patient adherence, along with emerging flavanones, pose exciting prospects. Despite challenges, flavanones hold promise, and future research must address gaps for meaningful clinical applications in cancer therapy.

CHAPTER SEVEN

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