CAPITAL UNIVERSITY OF SCIENCE AND TECHNOLOGY, ISLAMABAD

Exploration of *Prunus armeniaca* Metabolites Inhibitory Role of Carbonic Anhydrase, Aldose Reductase and Estrogen Receptor Beta in Colon Cancer - An Insilico Study

by

Alina Jahangeer

A thesis submitted in partial fulfillment for the degree of Master of Science

in the

Faculty of Health and Life Sciences
Department of Bioinformatics and Biosciences

2025

I want to dedicate this achievement to my beloved parents, honorable teachers and friends who always encouraged and supported me in every crucial time during my studies to achieve my tasks and secure this degree.

CERTIFICATE OF APPROVAL

Exploration of *Prunus armeniaca* Metabolites Inhibitory Role of Carbonic Anhydrase, Aldose Reductase and Estrogen Receptor Beta in Colon Cancer - An Insilico Study

by

Alina Jahangeer

(MBS233009)

THESIS EXAMINING COMMITTEE

S. No.	Examiner	Name	Organization
(a)	External Examiner	Dr. M. Sheeraz Ahmad	PMAS-AAU, Rawalpindi
(b)	Internal Examiner	Dr. Rizwan ur Rehman	CUST, Islamabad

Dr. Muhammad Asad Anwar
Thesis Supervisor
October, 2025

Dr. Syeda Marriam Bakhtiar
Head
Dept. of Bioinfo. & Biosciences
October, 2025

Dr. Sahar Fazal
Dean
Faculty of Health & Life Sciences
October, 2025

Author's Declaration

I, **Alina Jahangeer** hereby state that my MS thesis titled "**Exploration of *Prunus armeniaca* Metabolites Inhibitory Role of Carbonic Anhydrase, Aldose Reductase and Estrogen Receptor Beta in Colon Cancer - An In-silico Study**" is my own work and has not been submitted previously by me for taking any degree from Capital University of Science and Technology, Islamabad or anywhere else in the country/abroad.

At any time if my statement is found to be incorrect even after my graduation, the University has the right to withdraw my MS Degree.

(Alina Jahangeer)

Registration No: MBS233009

Plagiarism Undertaking

I solemnly declare that research work presented in this thesis titled "**Exploration of *Prunus armeniaca* Metabolites Inhibitory Role of Carbonic Anhydrase, Aldose Reductase and Estrogen Receptor Beta in Colon Cancer - An Insilico Study**" is solely my research work with no significant contribution from any other person. Small contribution/help wherever taken has been duly acknowledged and that complete thesis has been written by me.

I understand the zero tolerance policy of the HEC and Capital University of Science and Technology towards plagiarism. Therefore, I as an author of the above titled thesis declare that no portion of my thesis has been plagiarized and any material used as reference is properly referred/cited.

I undertake that if I am found guilty of any formal plagiarism in the above titled thesis even after award of MS Degree, the University reserves the right to withdraw/revoke my MS degree and that HEC and the University have the right to publish my name on the HEC/University website on which names of students are placed who submitted plagiarized work.

(Alina Jahangeer)

Registration No: MBS233009

Acknowledgement

First, thanks to the most powerful and most beneficial Allah Almighty, who inculcated skills, knowledge, and endless effort in me to reach here and accomplish my research work. A special thanks to my thesis supervisor "**Dr. Asad Anwar**" for his help, support, interest, and valuable time. Thanks for supervising and motivating me throughout the way to accomplish this thesis. I am grateful to my institute, Capital University of Science and Technology (CUST) Islamabad. I would like to thank my family for providing me with unfailing support and continuous encouragement. I would like to express my cordial gratitude towards my parents and siblings. I would like to thank my friends for helping and motivating me. Finally, I appreciate all the encouragement I have received from several others who have been involved in some way or another with this research work for the accomplishment of my tasks in hand.

(Alina Jahangeer)

Abstract

Colon cancer is a complex disease marked by the uncontrolled proliferation of cells in the colon, often developing from benign adenomatous polyps. The progression of colon cancer involves a combination of genetic, epigenetic, and environmental factors, including inflammation and oxidative stress, which significantly contribute to its pathogenesis. As the global incidence of colon cancer continues to rise, particularly in developing countries, research into effective and safe strategies for prevention and treatment is becoming increasingly critical. *Prunus armeniaca* (apricot) emerges as a vital source of bioactive metabolites, offering a variety of compounds with significant potential for therapeutic applications thus associated with various health benefits. This study investigates the potential anticancer effects of apricot metabolites against colon cancer using an insilico approach, aiming to uncover their mechanisms of action and efficacy in combating this prevalent disease. Quercetin, hyperoside, kaempferol, caffeic acid, limonene, catechins, geraniol, folate, cyanidin and chlorogenic acid were selected as potential metabolites and examined for their interactions with key cancer-related proteins such as carbonic anhydrase 9, aldose reductase and estrogen receptor beta. Carbonic anhydrase contributes to an acidic environment that may promote the growth of colon cancer, while aldose reductase increases oxidative stress, aiding cancer cell survival. Estrogen receptor beta plays a role in regulating cell growth. The 3D structure of the target proteins and the ligands served as the input for docking. The best ligand was selected based on drug likeness, ADMET analysis, docking score, and interactions profile. The research underscores the promising ADMET profile of hyperoside, concerning high water solubility, good intestinal absorption, and minimal toxicity. The docking scores and protein-ligand interactions shown by hyperoside are also considerable with all proteins i.e. carbonic anhydrase, aldose reductase and estrogen receptor beta. To check further effectiveness of hyperoside, it was compared with the commercially available anticancer drug fluorouracil. A comparison of all drug-like characteristics showed that hyperoside is comparable with fluorouracil in ADMET analysis while the docking score and interaction profile of hyperoside are much better than

fluorouracil. So, it is concluded here that hyperoside can prove itself as a potential anti-cancer drug candidate in the context of colon cancer in future therapeutics.

Keywords: Anticancer, Hyperoside, ADMET Profile, Bioactive Metabolites, Therapeutics

Contents

List of Figures

List of Tables

Abbreviations

5-FU	Fluorouracil
ADMET	Absorption, distribution, metabolism, excretion, toxicity
APC	Adenomatous polyposis coli
AR	Aldose reductase
BBB	Blood brain barrier
CA 9	Carbonic anhydrase
CB-dock	Cavity detection guided blind docking
CNS	Central nervous system
CYP2D6	Cytochrome P450 2D6
EGCG	Epigallocatechin gallate
EGFR	Epidermal growth factor receptor
ERB	Estrogen receptor beta
GALT	Gut-associated lymphoid tissue
GRAVY	Grand average of hydropathicity
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
MW	Molecular weight
NR	Negative residues
PDB	Protein data bank
PR	Positive residues
VDss	Volume of distribution at steady state
WHO	World Health Organization

Chapter 1

Introduction

Colon cancer, or colorectal cancer, is a significant health issue around the world. Its rising occurrence has made it one of the leading causes of cancer-related illness and death. This complex disease not only affects patients physically but also creates emotional and financial stress for them, their families, and healthcare systems. In recent years, developing countries have seen a sharp increase in new cases, largely due to urban growth, changes in diet, and less physical activity. Unlike infectious diseases that show clear symptoms, colon cancer often develops quietly over many years, making early detection difficult. As benign growths turn into malignant tumors slowly, many chances for prevention are often missed. This underscores the need for strong awareness campaigns, accessible screening programs, and affordable preventive strategies that fit cultural contexts [1].

The development of colon cancer typically follows a process known as the adenoma-carcinoma sequence. In this process, normal cells in the colon undergo a series of genetic changes that eventually lead to cancer. This transformation can take years or even decades. It starts with the formation of adenomatous polyps, which are small growths in the colon or rectum. While many of these polyps are harmless, some contain mutations that disrupt normal cell growth. The adenomatous polyposis coli gene is often among the first genes to be mutated in this process. This gene is crucial for cell adhesion and regulating the cell cycle; when it is inactive, cells can grow uncontrollably and accumulate more genetic changes. Over

time, some polyps may develop dysplasia, a precancerous stage with abnormal cell structures. This stage is critical, as early intervention could stop the disease from progressing [2].

As colon cancer progresses, more genetic mutations build up, speeding up tumor growth and making it more aggressive. One common mutation occurs in the KRAS oncogene, which happens early in the polyp stage and drives cell growth while preventing programmed cell death. Later on, the TP53 tumor suppressor gene is often turned off, removing a key barrier against uncontrolled cell growth. This allows cells to bypass normal checkpoints that prevent damaged DNA from being copied during cell division. These genetic changes often occur alongside alterations in the tumor environment, such as chronic inflammation and changes in blood vessel formation, which together promote cancer growth and spread. The accumulation of these changes shows that colon cancer is a complex, multi-step process influenced by both inherited genetic traits and environmental factors [3].

Environmental and lifestyle choices significantly affect the risk of colon cancer. Diets high in red and processed meats, sugar, and saturated fats have been linked to increased risk, while diets rich in whole grains, fruits, vegetables, and fiber seem to protect against it by reducing inflammation and improving gut health. Lack of physical activity increases risk by leading to obesity and insulin resistance. Other modifiable risk factors include smoking, excessive drinking, and insufficient intake of essential nutrients, all of which can influence colon cancer development [4]. Understanding how genetic factors interact with these environmental influences is vital for creating effective prevention strategies that consider both biological and behavioral aspects.

Worldwide, colon cancer is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths, according to the World Health Organization. In 2020, more than 1.9 million new cases and 935,000 deaths were reported, highlighting the significant challenge for health systems globally. High-income countries often have established screening programs like colonoscopy, while many low and middle income countries lack the resources for such measures [5]. This results in many cases being diagnosed at advanced stages, making treatment

more difficult and costly. The difference in survival rates between early and late diagnoses emphasizes the critical need for prevention and early detection in global cancer control efforts.

Standard treatment for colon cancer usually involves a mix of surgery, chemotherapy, and radiation therapy, depending on the tumor's stage and location. Surgery is the main treatment for localized cancer, involving the removal of the affected bowel section and nearby lymph nodes. Chemotherapy is often given before or after surgery to target remaining cancer cells and lower the chances of recurrence. Radiation therapy is more commonly used for rectal cancer, but can also be applied in some colon cancer cases to shrink tumors or ease symptoms. While these treatments have improved survival rates, they often come with significant side effects like fatigue, nausea, and immune suppression. Additionally, cancer cells can become resistant to chemotherapy over time, making long-term treatment less effective [6].

Targeted therapies and immunotherapies have become significant advances in colon cancer treatment, offering more precise actions against specific cancer pathways. Drugs that block certain growth factors have shown benefits for some patients, and immune checkpoint inhibitors are promising for cancers with specific genetic features. However, these treatments can be expensive and carry risks, including cardiovascular issues and autoimmune reactions. The limitations of existing treatments highlight the urgent need for safer, more effective options [7]. In recent years, there has been growing interest in natural products as potential cancer treatments. Many compounds from plants have shown promising biological activity. Some current cancer drugs, like paclitaxel and vincristine, are derived from plants. Focusing on edible plants is particularly interesting because they provide both nutrition and therapeutic benefits. Unlike synthetic drugs, which can be highly toxic, plant-based compounds are generally better tolerated and may protect healthy tissues [8].

Apricot (*Prunus armeniaca*), part of the Rosaceae family, has attracted scientific interest for its potential in cancer prevention and treatment. Grown in regions from Central Asia to the Mediterranean, apricots have a long history in cooking

and medicine. Their delicious taste and rich nutritional content make them a staple in many diets. Beyond basic nutrition, apricots are rich in phytochemicals like flavonoids, phenolic acids, carotenoids, and terpenes, all of which may offer health benefits [9].

The diverse phytochemical composition of apricots allows them to target multiple biological processes in the body. Flavonoids such as quercetin and kaempferol are known for their antioxidant and anti-inflammatory properties, crucial in reducing oxidative stress, a factor that leads to cancer. Phenolic acids like caffeic acid and chlorogenic acid can inhibit cancer cell growth and enhance the effectiveness of chemotherapy. Terpenes like limonene and geraniol may help slow tumor growth by promoting cell death and influencing immune responses. Together, these compounds can act on various pathways involved in colon cancer [10].

Another significant component of apricots, dietary fiber, is crucial in avoiding colon cancer. By promoting regular bowel movements, fiber shortens the time that dangerous compounds come into touch with the intestinal lining. Additionally, it promotes the growth of good gut bacteria that generate butyrate and other short-chain fatty acids, which have anti-inflammatory and anti-cancer properties. By keeping the gut microbiome healthy, dietary fiber also strengthens immune function and overall health, lowering cancer risk.

Apricot kernels also contain bioactive compounds studied for their possible anti-cancer effects. Amygdalin, a compound found in the kernels, has been researched for its ability to inhibit tumor growth, but its use is controversial due to safety concerns. Other components from the kernels, like oils and proteins, have traditional medicinal uses for skin health and digestive issues. While not all these uses have been scientifically proven, they highlight the cultural importance and versatility of apricot products [11]. Research on apricot bioactives has shown strong antioxidant activity, which is vital for countering the harmful effects of reactive oxygen species. High oxidative stress can lead to DNA damage and cancer progression. By neutralizing free radicals, antioxidants in apricots help protect cells and reduce mutation rates [12]. This protective effect is particularly relevant for those exposed to chronic inflammation or environmental toxins.

Flavonoids such as quercetin and hyperoside do more than just neutralize free radicals; they also influence signaling pathways related to inflammation and cell death. For instance, quercetin can inhibit a protein called NF-κB, which promotes inflammation and cell survival. By reducing NF-κB activity, quercetin may help suppress inflammation and make cancer cells more susceptible to dying. These dual actions make flavonoids appealing candidates for cancer treatment strategies [13]. Phenolic acids also enhance apricot's anticancer potential. Caffeic acid can interfere with DNA synthesis in cancer cells and stop the formation of new blood vessels that tumors need to grow. Chlorogenic acid has similar effects and can influence glucose metabolism, which may affect cancer cell survival due to their high energy needs [14]. These findings suggest that apricot-derived phenolic compounds could serve as multi-target agents in cancer prevention and treatment. Terpenes like limonene and geraniol add another layer to apricot's health benefits. Limonene can enhance the body's ability to detoxify harmful substances, while geraniol can inhibit enzymes needed for cancer cell growth. By disrupting these processes, geraniol may help slow tumor growth and reduce the chance of spreading [15].

Apricots' vitamins and minerals also promote health and help prevent cancer. Folate is essential for DNA synthesis and repair, which helps stop cancer-causing mutations. Vitamin E protects cell membranes from damage, and beta-carotene, which the body turns into vitamin A, supports immune health. Together with apricot's phytochemical content, these nutrients make apricots a beneficial addition to diets aimed at reducing chronic disease risk, including colon cancer [16]. Targeting multiple pathways in colon cancer is an attractive approach because cancer usually results from various genetic errors and malfunctioning cellular systems. A fruit like apricot, which contains many compounds that act on different targets, might interfere with various stages of cancer development. Some compounds may prevent DNA damage, others could reduce inflammation, and some might enhance the effectiveness of chemotherapy. This multi-target approach aligns well with modern cancer treatments, which increasingly recognize the need for combination therapies to improve patient outcomes [17]. In silico methods in biomedical research have speed up the process of screening plant compounds for potential therapeutic

uses. Molecular docking allows researchers to simulate how a small molecule, like a flavonoid, might interact with a protein involved in disease. This method gives valuable insights into how these compounds might work, often before any lab experiments are conducted [18]. For colon cancer, docking studies can help identify which apricot metabolites are likely to bind to important proteins, guiding further testing.

One such protein of interest is carbonic anhydrase IX, which is often found in low-oxygen areas of tumors, including colorectal cancers. This enzyme helps cancer cells survive in acidic environments. Inhibiting carbonic anhydrase IX can make cancer cells more susceptible to treatments. Apricot compounds that can bind to this enzyme may help disrupt the survival strategies of tumors [19]. Aldose reductase is another important target. This enzyme converts glucose to sorbitol and is linked to cancer progression by increasing oxidative stress and inflammation. High levels of aldose reductase have been found in colorectal cancer samples, indicating aggressive disease. Inhibiting this enzyme could help reduce damage and slow cancer growth [20].

Apricot bioactives that inhibit aldose reductase may address both metabolic and inflammatory aspects of colon cancer. Estrogen receptor beta is another potential target with protective effects against colorectal cancer. Unlike estrogen receptor alpha, which can promote cancer growth, estrogen receptor beta may help reduce cell growth and promote cell death in colon cells. Compounds in apricots can act as phytoestrogens, influencing these receptors. By targeting estrogen receptor beta, these compounds might help balance disrupted signaling pathways in cancer [21].

While the potential of apricot bioactives in cancer prevention and therapy is promising, it's important to understand how well these compounds can be absorbed and used by the body. Not all dietary compounds are effectively absorbed, and some may be quickly broken down or eliminated before reaching their targets. Factors like food preparation and interactions with other foods can affect how these compounds work. New techniques, like microencapsulation, are being studied to improve the stability and absorption of plant compounds, which could

lead to more effective apricot-based supplements [22]. Apart from their direct effects on cancer, apricots can improve overall health in ways that may lower cancer risk. For instance, maintaining a healthy weight is a known protective factor against colon cancer, and the low-calorie, high-fiber nature of apricots supports weight management. Their natural sweetness can satisfy cravings for sweets while providing essential nutrients [11]. By helping manage appetite and blood sugar levels, apricots may prevent obesity and related metabolic issues, both of which increase the risk of colon cancer.

Research has shown that populations eating diets rich in fruits and vegetables tend to have lower rates of many cancers, including colorectal cancer. While these studies don't prove direct cause-and-effect relationships, they highlight the importance of diet in disease prevention. In this context, apricots stand out for their nutrient density and unique combination of phytochemicals. Adding apricots to daily meals can be simple, like swapping processed desserts for fresh or dried apricots. Over time, these small dietary changes can lead to significant reductions in cancer risk [23]. Another benefit of focusing on apricots is their availability and adaptability to different climates. Unlike some medicinal plants that are restricted to specific regions, apricots are cultivated all throughout the planet making them accessible to diverse populations. Their short growth cycle and established market presence also make apricots suitable for fresh consumption and products like juices and jams. From a public health perspective, including apricots in cancer prevention strategies could be especially effective in low-resource settings. These areas often lack the means for large-scale screening and advanced treatments. Therefore, population-level dietary interventions become crucial. Encouraging the cultivation and consumption of locally grown apricots can improve community nutrition, boost local economies, and reduce cancer risk. This approach aligns with sustainable development goals that connect health, food security, and economic stability [24].

Historically, apricots and other stone fruits have been used in traditional medicine across various cultures. For instance, in traditional Chinese medicine, apricot seeds are used for respiratory issues, while in Middle Eastern cultures, apricot-based

remedies are suggested for digestive health. Ancient Egyptians used apricots to relieve constipation and promote vitality. Although not all these uses have been scientifically proven, they provide a foundation for further research into apricot's health benefits. Apricots also have a pleasant taste that encourages regular consumption, which is important for dietary interventions. Unlike some medicinal plants that may taste bitter, apricots can be enjoyed in many ways, whether fresh, dried, or in various recipes. This versatility makes it easy to include them in everyday diets, enhancing long-term adherence to healthy eating. Exploring apricot's potential against cancer also helps us understand how plants interact with humans on a molecular level. For example, studying how gut bacteria process apricot phytochemicals could reveal new health benefits. The regulation of immunological responses and inflammation is significantly influenced by the gut microbiota [16]. Apricot fibers and polyphenols may have a variety of impacts outside of the colon via affecting gut microbes [16].

Another important factor is the potential for different compounds in apricots to work together. Isolated phytochemicals may show limited effects, but when combined as they naturally occur in the fruit, they can produce stronger results. For instance, antioxidants from different groups may support each other's action after neutralizing free radicals, extending their protective effect. This synergy emphasizes the value of studying whole foods rather than just individual compounds. The safety of apricots, especially the fruit itself, is generally very good, making them a great option for long-term diets. However, caution is needed with apricot kernels, which can release cyanide and be toxic if eaten in large amounts. Public health advice focuses on promoting safe consumption of apricot products while discouraging risky practices, ensuring the benefits of eating apricots are enjoyed without unnecessary dangers. Creating apricot-based functional foods or supplements will require teamwork between agricultural scientists, food technologists, and medical researchers [25]. Choosing the right apricot varieties, perfecting processing methods to keep bioactive compounds intact, and conducting thorough clinical trials are all vital steps. New techniques in metabolomics will help pinpoint the specific compounds with anticancer effects. Such collaborative research could lead to better dietary recommendations and health-promoting apricot products.

Incorporating apricots into colon cancer prevention strategies aligns with the broader trend in nutrition science that emphasizes whole foods and plant-based diets. Rather than just relying on drugs after disease occurs, these approaches aim to create a body environment less prone to cancer from the start. By combining knowledge from various fields, researchers can create comprehensive models for preventing disease. Apricots thus provide a strong example of how a widely available fruit can be used for both nutrition and health benefits [16].

Apart from their potential in preventing cancer, apricots can also support patients who are currently undergoing treatment. Their rich nutrient content can help maintain health during therapy, especially when appetite is low. While fiber helps with digestion and relieves constipation, a typical side effect of painkillers, natural sugars provide mild energy.

Antioxidants may also lessen radiation and chemotherapy-induced oxidative stress, which might lessen treatment-related weariness. Patients' quality of life and treatment compliance may both be enhanced by these supporting effects, which may ultimately lead to improved outcomes.

As research on apricot phytochemicals advances, the role of diet alongside standard medical care becomes clearer. Nutrition has traditionally been seen as a way to maintain general health, but modern cancer care recognizes its potential to influence disease progression directly. This shift opens up opportunities for more integrated care models where dietary advice is tailored to a patient's specific cancer type and treatment plan. For colon cancer, where the disease is directly affected by what we eat, the impact of food-derived compounds can be significant.

Apricots, with their mix of beneficial compounds, fit well into this integrated approach. The growing research on plant-based compounds for cancer therapy highlights the need for well-designed studies. While laboratory and animal studies provide important insights, human trials are essential to confirm safety and effectiveness [26]. For apricots, these trials should consider factors like ripeness and preparation, which can affect the phytochemical content. Standardizing these variables is crucial for producing reliable results that can inform public health

guidelines. Without rigorous research, promising findings risk being confined to the lab instead of benefiting patients.

Future research should also explore how apricot bioactives interact with standard cancer treatments. Some compounds may enhance the effects of chemotherapy, while others might interfere with drug metabolism. Understanding these interactions is essential to ensure dietary changes support, rather than hinder, medical treatments. Early evidence suggests that some apricot compounds could work well with standard drugs, potentially allowing for lower doses and less toxicity. Confirming these interactions could significantly improve personalized cancer care. The sustainability of producing apricot-based products is another important factor to consider. Apricots grow well in temperate climates, and improvements in farming techniques have expanded their growing regions [27]. However, increasing production for health purposes requires careful management to maintain quality and ensure fair distribution. Using sustainable farming practices would help protect the environment while supporting local economies. The increasing need for efficient and environmentally friendly health solutions is in line with these factors.

Beyond the fruit, apricot leaves, flowers, and bark may contain bioactive compounds worth studying. Traditional medicine has used various parts of the apricot tree for many health issues. While research has mainly focused on the fruit and seeds, looking into these other parts could uncover new therapeutic benefits. This holistic approach to using plants maximizes what we can gain from each harvest while reducing waste. When considering apricots in cancer prevention, it's important to remember that no single food can eliminate the risk of disease. The aim is to create dietary patterns that together reduce exposure to harmful substances, boost immune health, and maintain metabolic balance [28].Public education is essential for promoting apricots as part of a diet that helps prevent cancer. While scientific evidence supports their benefits, it must be communicated clearly and in a culturally relevant way. Nutrition campaigns should focus on practical tips for including apricots in everyday meals, highlighting their freshness, serving sizes, and safe preparation methods. Collaborating with local chefs, community leaders, and healthcare providers can help tailor these messages to different audiences,

making them more effective. Educating people is a key step in changing eating habits toward healthier choices.

Research on apricots and colon cancer illustrates the growing field of nutritional oncology. This area combines knowledge from molecular biology, pharmacology, epidemiology, and food science to understand how diet affects cancer risk and development. It connects general dietary recommendations with personalized treatment strategies. Studying the bioactive compounds in *Prunus armeniaca* can enhance both scientific knowledge and practical health solutions. As this field progresses, such research is likely to play a bigger role in cancer prevention and treatment. Advances in technology are expanding the tools available for researching plant-based compounds. Methods like high-throughput screening and metabolomic profiling allow for quick identification and analysis of bioactive compounds in complex mixtures. These techniques can help map the full range of phytochemicals in apricots, identifying both major and minor compounds with potential health benefits. Combining these methods with computational modeling creates an effective platform for discovering and optimizing natural cancer-fighting agents. This integration of technology and plant science is helping to unlock the full health benefits of everyday foods [29].

The idea of using food as medicine is gaining renewed attention in cancer care. This approach focuses on using dietary components to prevent disease or support treatment, rather than relying solely on medical interventions. Apricots serve as a great example of how a common food can be re-evaluated through modern research to uncover new health benefits. By basing dietary recommendations on solid science, healthcare providers can give patients evidence-based advice that complements traditional treatments and fits their preferences. Including apricots in strategies for preventing colon cancer aligns with global health priorities that stress the importance of nutrition in controlling non-communicable diseases. Organizations like the World Health Organization promote increased fruit and vegetable consumption as a key part of health promotion. Integrating research on foods like apricots into broader health initiatives could refine guidelines and inspire targeted actions. By emphasizing both the nutritional and health benefits

of such foods, public health campaigns can effectively encourage dietary changes at both individual and community levels [30].

Promoting apricot cultivation and consumption can have multiple economic benefits. For farming communities, especially those that grow apricots, increased demand from health-conscious consumers can boost local economies. For healthcare systems, dietary prevention strategies could lower the rates of expensive diseases like colon cancer. Although quantifying short-term savings can be challenging, the long-term impact on public health budgets could be significant. These economic factors support the need for research and policies that promote nutrient-rich foods in daily diets. Exploring the role of *Prunus armeniaca* in preventing and treating colon cancer is a promising intersection of nutrition science, oncology, and public health. By using the natural complexity of plant compounds, researchers can develop strategies that are both scientifically sound and widely accessible. Focusing on whole foods ensures that these strategies provide additional health benefits, supporting overall well-being. While there are still challenges with standardization and clinical validation, current research suggests that effective solutions are within reach. Ongoing collaboration across disciplines will be crucial to maximizing apricots' potential in cancer care [31].

This research aims to identify and thoroughly understand the specific bioactive substances present in apricots that exhibit anticancer effects, particularly in the context of colon cancer treatment. By systematically reviewing existing studies and conducting in silico-based research, the goal of this thesis is to identify the processes by which these substances carry out their preventative anti-cancer actions. This approach can lead to better health outcomes for individuals who are at risk of colon cancer.

1.1 Problem Statement

Colon cancer is a growing health concern worldwide, with increasing prevalence, especially in developing countries. Traditional treatments often come with significant side effects, leading to a need for safer, more effective alternatives.

1.2 Hypothesis

The *Prunus armeniaca* bioactive metabolites might have an active anti-cancerous role in the context of colon cancer.

1.3 Aim and Objectives

This research aims to explore potential bioactive metabolites from apricot showing anti-cancer properties to combat colon cancer.

This research entails the following objectives:

- To screen apricot metabolites with anti-cancerous properties.
- To analyze the interaction between specific apricot metabolites and the desired target proteins i.e., carbonic anhydrase, aldose reductase and estrogen receptor beta.
- To identify the best docked metabolite as an inhibitory molecule having colon cancer.

Chapter 2

Literature Review

Colon cancer, also known as colorectal cancer, represents a major public health challenge globally. It is distinguished by the uncontrolled growth of colon or rectum cells, often commencing as benign adenomatous polyps that can progressively develop into malignant tumors. The World Health Organization (WHO) has called attention to the growing prevalence of colon cancer as a serious health issue, especially in developing countries where the illness is more common due to dietary changes, lifestyle changes, and a lack of early screening. Treatment methods need to be reevaluated in light of the rising prevalence of colon cancer. Although traditional therapies like radiation, chemotherapy, and surgery are frequently employed, they often come with significant side effects and limitations. Consequently, interest in investigating alternative medicines is increasing, particularly those derived from natural products. This literature review focuses on apricot (Prunus armeniaca), a fruit traditionally valued for its nutritional benefits, as a potential source of bioactive substances that may possess anticancer properties, especially against colon cancer. Recent studies have indicated that apricot phytochemicals may be essential for modifying cancer pathways, thereby offering an alternative approach to traditional cancer therapies.

2.1 Colon Cancer

Colon cancer is defined as a malignant tumor that originates in the epithelial lining of the colon or rectum. The tumor can develop from various types of polyps, mostly adenomatous polyps, which are cancer-precursors. These polyps may experience a number of genetic alterations if treatment is not received, leading to the transformation from benign to malignant status.

The progression of colon cancer is often asymptomatic in its early stages, which underscores the importance of routine screening, especially for individuals over the age of 45 or those with a family history of colorectal cancer [32].

The disease can infiltrate deeper layers of the colon, including the muscularis propria and serosa, potentially spreading to adjacent tissues and distant organs through lymphatic and hematogenous routes. Late-stage colon cancer significantly complicates treatment and adversely affects patient prognosis, Improving survival rates requires early identification and management [33].

2.2 Prevalence

About 10% of all cancer cases worldwide are colorectal cancer, making it the third most frequent kind of cancer. In 2020, over 1.9 million new cases were reported, with estimates of 935,000 deaths attributed to the disease. The incidence of colorectal cancer varies significantly across different regions, influenced by factors such as lifestyle, diet, genetic predisposition, and access to healthcare services [34].

In Pakistan, the prevalence of colon cancer has been on the rise, particularly among urban populations. A recent study reported an incidence rate of approximately 8.8 per 100,000 individuals, with a notable increase among younger populations due to changing dietary patterns and lifestyle choices. The lack of awareness regarding screening and preventive measures further exacerbates the situation, leading to late diagnoses and poorer outcomes [35].

2.3 Normal Mechanism of the Colon

The colon, or large intestine, is vital for several physiological processes that contribute to digestive health and overall homeostasis, as shown in figure 2.1. Understanding its various functions helps underscore its importance in maintaining bodily balance.

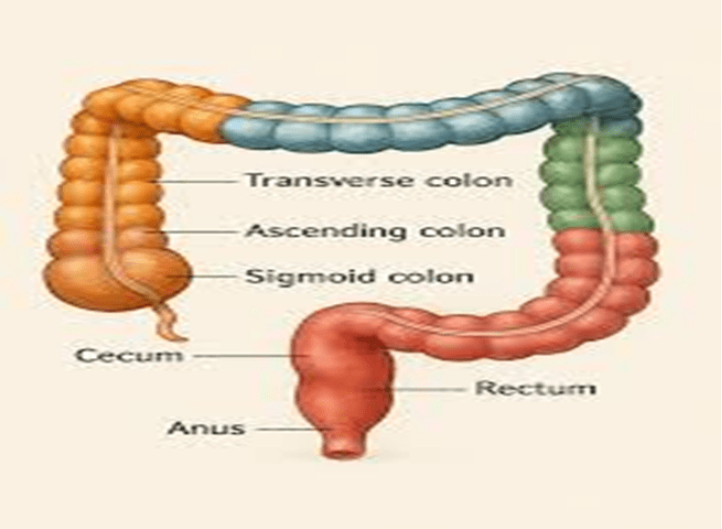


FIGURE 2.1: Anatomy of Colon. The image shows the human large intestine, including the cecum, ascending colon, transverse colon, sigmoid colon, rectum, and anus. It functions mainly to absorb water and nutrients, compact waste into feces, and enable its removal from the body. Each section is crucial for effective digestion and waste management.

2.3.1 Water Absorption

The colon's primary function is to reabsorb water from indigestible food matter. As the contents of the digestive tract move from the small intestine to the colon, they contain a significant amount of fluid, approximately 1.5 to 2 liters daily. The colon has specialized epithelial cells that facilitate the absorption of water and electrolytes. Water absorption occurs via osmosis, driven by the osmotic gradient created by solutes such as sodium and chloride ions. The presence of water channels in the colon's epithelial cells enhances this process, allowing for efficient water reabsorption. By reabsorbing water, the colon helps maintain hydration and electrolyte balance, which are crucial for various physiological functions, including

temperature regulation, nerve conduction, and muscle function. Dehydration can lead to complications such as constipation or fecal impaction, emphasizing the colon's role in fluid balance [36].

2.3.2 Waste Formation

The colon is responsible for compaction and storage of waste products, which consist of undigested food, bacteria, and sloughed-off cells from the intestinal lining. Feces are primarily composed of water about 75%, with the remainder consisting of bacteria, dietary fiber, and other organic and inorganic substances. The colon absorbs water and electrolytes from this material, transforming it into a solid or semi-solid state. The colon serves as a reservoir for fecal matter until defecation. The rectum, the final section of the colon, stores feces temporarily until the anal sphincters relax, allowing for controlled elimination. This process is coordinated by neural signals and reflects the colon's role in maintaining bodily waste management [37].

2.3.3 Gut Flora Maintenance

The colon is home to a diverse microbiome, comprising trillions of microbes that are important for digesting and general well-being. The gut microbiota includes various species of bacteria, fungi, and viruses, with a diversity that can be influenced by diet, age, and health status. A balanced microbiome is crucial for optimal digestive function and overall health. Human enzymes cannot digest many food fibers, However, they can be fermented by intestinal microbes. This fermentation process produces short-chain fatty acids, such as butyrate, which provide anti-inflammatory and energy-giving qualities to colon cells. Additionally, they maintain intestinal health and regulate metabolism. Gut bacteria synthesize essential vitamins, such as vitamin K and certain B vitamins (like B12 and folate). These vitamins are important for blood coagulation and various metabolic processes, highlighting the critical relationship between gut flora and nutrient absorption [38].

2.3.4 Immune Function

The colon plays a vital role in the immune system, acting as a barrier against pathogens and helping to regulate immune responses. The epithelial lining of the colon forms a physical barrier that prevents harmful substances and pathogens from entering the bloodstream. Tight junctions between epithelial cells maintain this barrier's integrity.

The gut-associated lymphoid tissue (GALT) within the colon is a crucial component of the immune system. It helps recognize and respond to pathogens while maintaining tolerance to non-harmful antigens, such as food proteins and commensal bacteria. This balance is vital for preventing inflammatory diseases [39].

2.3.5 Gas Production and Elimination

Gases including carbon dioxide, methane, and hydrogen are produced by gut bacteria when they ferment undigested carbohydrates. Bloating and flatulence can result from the buildup of these gasses. While gas production is a normal part of digestion, excessive gas can indicate imbalances in gut flora or dietary issues.

The colon has mechanisms to regulate gas expulsion, which involves the relaxation of the anal sphincter and coordinated muscular contractions of the colon. This process helps maintain comfort and digestive efficiency [40].

2.4 Diseases of the Colon

The colon is susceptible to a range of diseases that can lead to significant health complications. Each condition has unique characteristics, symptoms, and management strategies. The most prevalent diseases affecting the colon include Inflammatory Bowel Disease, diverticulitis, colorectal cancer, irritable bowel syndrome, ischemic colitis, and others.

2.4.1 Inflammatory Bowel Disease

Inflammatory Bowel Disease comprises chronic inflammatory conditions primarily affecting the gastrointestinal tract, with Crohn's disease and ulcerative colitis being the two main types. Both conditions are characterized by an inappropriate immune response, leading to inflammation of the intestinal lining as shown in figure 2.2.

2.4.2 Crohn's Disease

Crohn's disease can affect any part of the gastrointestinal tract, although it most commonly involves the ileum, the last section of the small intestine and the colon. The inflammation can penetrate the entire thickness of the intestinal wall, leading to complications such as narrowing of the intestine, abscesses, and abnormal connections between organs. Symptoms often include recurrent abdominal pain, bloody diarrhea, weight loss, and fatigue.

Patients may also experience extraintestinal manifestations, such as arthritis, skin rashes, and eye inflammation, due to the systemic effects of chronic inflammation. Management of Crohn's disease typically involves anti-inflammatory medications, immunosuppressants, and biologics that target specific components of the immune response. In extreme situations, surgery could be required to remove intestinal segments that are impacted or to treat issues like strictures or fistulas [41].

2.4.3 Ulcerative Colitis

Ulcerative colitis primarily affects the colon and rectum, with inflammation confined to the mucosal layer. Symptoms include abdominal cramping, bloody diarrhea, and urgency to defecate, which can significantly impact quality of life. The disease often presents in episodes, with periods of remission interspersed with flare-ups. Long-term ulcerative colitis increases the risk of developing colorectal cancer, particularly after ten years of disease duration. Management strategies typically include anti-inflammatory drugs, immunosuppressants, and biologics. In

cases where medical therapy fails, surgical options such as colectomy may be considered as a curative approach [42].

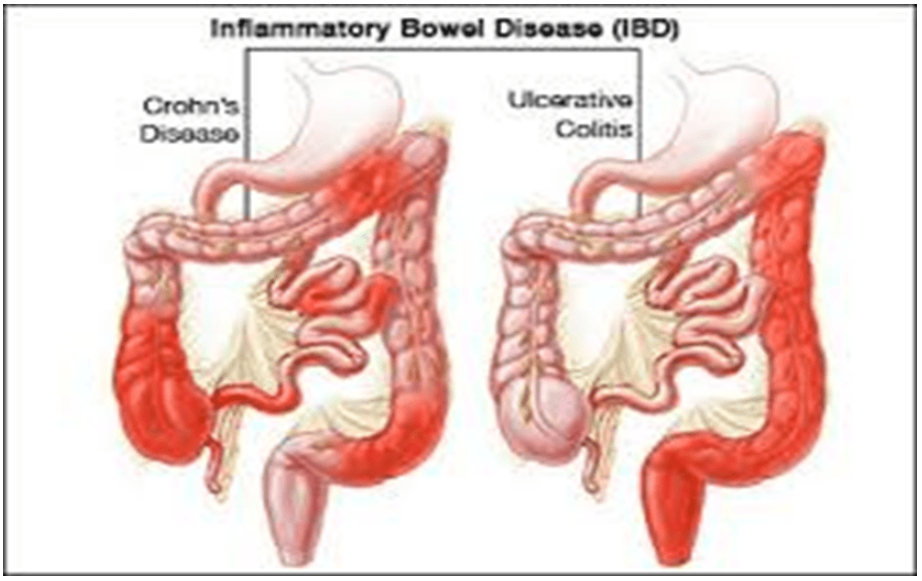


FIGURE 2.2: Inflammatory bowel disease. The figure depicts inflammatory bowel disease, highlighting two types: Crohn's disease and ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract with deeper inflammation, while ulcerative colitis primarily targets the colon and rectum, causing inflammation in the inner lining. Both conditions lead to symptoms like abdominal pain & diarrhea.

2.4.4 Diverticulitis

Diverticulitis occurs when diverticula, small pouches that can form in the colon wall, become inflamed or infected. This condition has become increasingly common, especially in Western countries where diets are often low in fiber. The pathophysiology of diverticulitis involves increased pressure within the colon, leading to the formation of these pouches. Symptoms typically include left lower quadrant abdominal pain, fever, and changes in bowel habits, such as diarrhea or constipation. Complications of diverticulitis can be severe and include abscess formation, perforation, and peritonitis. The treatment may include antibiotics for mild cases, while severe or recurrent cases might necessitate surgical intervention to remove the affected segment of the colon. Post-operative management often involves dietary modifications to prevent recurrence, such as increasing fiber intake and maintaining adequate hydration [43].

2.4.5 Colorectal Cancer

Colorectal cancer is a leading cause of cancer-related deaths worldwide, arising from adenomatous polyps that undergo malignant transformation. Risk factors include age, family history, genetic syndromes, However, they can be fermented by intestinal microbes. This fermentation process produces short-chain fatty acids, such as butyrate, which provide anti-inflammatory and energy-giving qualities to colon cells. Additionally, they maintain intestinal health and regulate metabolism. Changes in bowel patterns, blood in the stool, inexplicable weight loss, and discomfort in the abdomen are some of the symptoms. Since colorectal cancer is very curable when detected early, routine screening, including colonoscopies, is essential for improving results. Depending on the disease's stage, treatment options usually consist of radiation therapy, chemotherapy, and surgical resection [44].

2.4.6 Irritable Bowel Syndrome

Irritable Bowel Syndrome is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits, including diarrhea and constipation, without any identifiable organic cause. The exact etiology of Irritable Bowel Syndrome remains unclear, but it is thought to involve a combination of genetic predisposition, gut-brain interactions, and dysbiosis of the gut microbiota. Bloating, gas, and a feeling of incomplete evacuation following bowel motions are some of the symptoms, which can differ greatly from patient to patient. Management of Irritable Bowel Syndrome focuses on symptom relief and may include dietary changes such as increasing fiber intake, stress management techniques, and medications to address specific symptoms like antispasmodics or laxatives [45].

2.4.7 Ischemic Colitis

Ischemic colitis occurs when blood flow to a portion of the colon is reduced, often due to narrowed or blocked blood vessels. This condition is more common in older adults and can be precipitated by factors such as atherosclerosis, low blood

pressure, or certain medical procedures. Symptoms typically include sudden onset of abdominal pain, cramping, and bloody diarrhea.

If blood flow is not restored, ischemic colitis can lead to tissue death and perforation of the colon, necessitating urgent medical intervention. Treatment may involve hospitalization, intravenous fluids, and sometimes surgery to remove the affected portion of the colon [46].

2.4.8 Colonic Polyps

Colonic polyps are growths that can form on the lining of the colon. While many polyps are benign, certain types such as adenomatous polyps have the potential to become cancerous over time. Regular screening through colonoscopy is essential for the early detection and removal of polyps to prevent colorectal cancer [47].

2.4.9 Celiac Disease

Celiac disease is an autoimmune disorder triggered by the ingestion of gluten, leading to inflammation and damage to the small intestine.

While primarily affecting the small intestine, it can also have secondary effects on the colon, resulting in symptoms such as weight loss, diarrhea, and nutritional deficiencies.

Diagnosis is made through serological tests and intestinal biopsy, and management involves strict adherence to a gluten-free diet [48].

2.4.10 Colon Infections

Infections of the colon can be caused by various pathogens, including bacteria such as Clostridium difficile, viruses, and parasites. These infections can result in symptoms including fever, diarrhea, and stomach ache. Treatment often includes antibiotics or antiparasitic medications, depending on the causative agent [49].

2.5 Formation of Colon Cancer

Colon cancer typically evolves through a series of genetic and epigenetic changes that transform normal colonic epithelial cells into malignant tumor cells. This progression is often gradual, taking years to decades, and is influenced by both genetic predispositions and environmental factors. Understanding this multi-step process is crucial for developing preventive strategies and targeted therapies. The majority of colon cancers arise from adenomatous polyps through a well-documented sequence known as the adenoma-carcinoma sequence [50]. The figure 2.3 illustrates the progression from benign to malignant states and involves several critical stages.

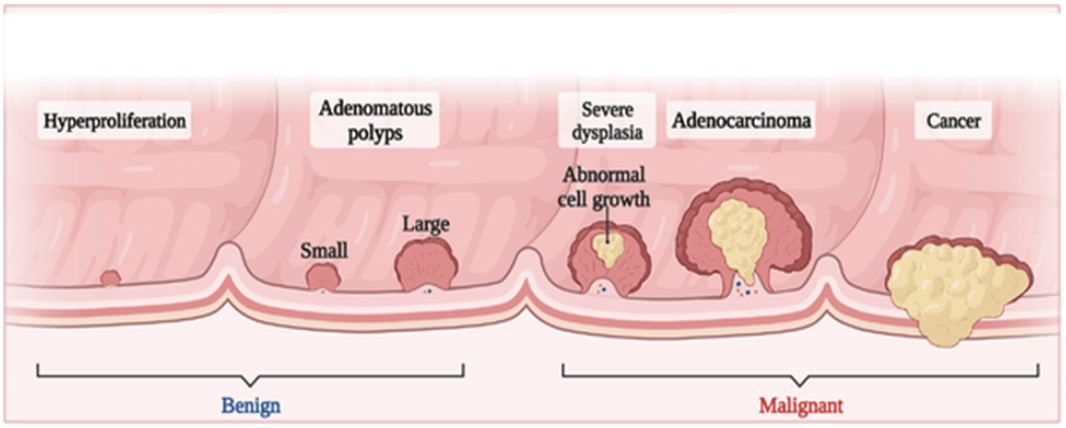


FIGURE 2.3: Formation of colon cancer. The figure outlines the progression of colon cancer, beginning with hyperproliferation of cells. It illustrates the formation of adenomatous polyps, which can grow larger and lead to severe dysplasia. This process can ultimately result in adenocarcinoma, marking the transition from benign conditions to malignant cancer in the colon.

2.5.1 Formation of Adenomatous Polyps

The initial step in this progression is often a mutation in the APC (Adenomatous Polyposis Coli) gene, a key tumor suppressor gene that regulates cell adhesion and growth. Mutations in APC disrupt this regulation, leading to unchecked cell proliferation and the formation of adenomatous polyps. As these polyps develop, they may undergo dysplasia, characterized by abnormal cell morphology and increased proliferation rates. Dysplastic cells exhibit a loss of normal architectural organization, which is a precursor to carcinoma [51].

2.5.2 Progression to Carcinoma

As polyps grow, they can accumulate additional mutations in other key genes, notably KRAS. This oncogene is frequently mutated in colorectal cancers and promotes cell division and survival. KRAS mutations often occur in early adenomas and are associated with the progression to malignant tumors. The tumor suppressor gene TP53 is critical for regulating the cell cycle and apoptosis. Mutations in TP53 typically arise in advanced adenomas and are linked to genomic instability, facilitating further tumor progression. Eventually, the combination of mutations and dysregulation of growth pathways leads to the invasion of the basement membrane, marking the transition from carcinoma in situ to invasive cancer [52].

2.5.3 Molecular Mechanisms and Pathways

The transition from normal colonic epithelium to invasive cancer involves several molecular mechanisms and pathways. Many colorectal cancers exhibit chromosomal instability, characterized by an increased rate of chromosomal gains and losses. This instability leads to further genetic mutations and promotes tumor progression [53]. Some colorectal cancers, especially those associated with Lynch syndrome, exhibit microsatellite instability due to defects in DNA mismatch repair. This leads to the accumulation of mutations in repetitive DNA sequences, contributing to tumorigenesis. The epidermal growth factor receptor (EGFR) pathway is involved in cell proliferation and survival. Overactivation of this pathway due to mutations or overexpression of EGFR can contribute to tumor growth and resistance to targeted therapies [54].

2.5.4 Carbonic Anhydrase 9

Several specific proteins and enzymes play pivotal roles in the development and progression of colon cancer. Carbonic anhydrase (CA 9) is an enzyme that catalyzes the reversible hydration of carbon dioxide, playing a crucial role in maintaining acid-base balance, particularly in the tumor microenvironment. CA 9 is

often upregulated in hypoxic conditions, which are common in rapidly growing tumors. By facilitating the conversion of carbon dioxide to bicarbonate, CA 9 helps maintain a favorable pH, allowing cancer cells to survive in acidic environments.

Overexpression of CA 9 has been associated with poor prognosis in colorectal cancer, as it correlates with increased tumor aggressiveness and metastatic potential [55].

2.5.5 Aldose Reductase

Aldose reductase is an enzyme in the polyol pathway that converts glucose into sorbitol. Its role in cancer biology is becoming increasingly recognized. Aldose reductase can contribute to oxidative stress by depleting NADPH, which is crucial for cellular antioxidant defenses.

Increased oxidative stress can lead to DNA damage and promote tumorigenesis. Aldose reductase is frequently overexpressed in colorectal cancer tissues, according to studies enhancing the survival and proliferation of cancer cells in adverse environments [56].

2.5.6 Estrogen Receptor Beta

Estrogen Receptor Beta is one of the two main estrogen receptors, and its role in colorectal cancer is complex. Its activation has been shown to exert protective effects against colorectal cancer by promoting apoptosis and inhibiting cell proliferation. Its expression is often reduced in cancerous tissues, suggesting a potential tumor-suppressive role.

Estrogen Receptor Beta can regulate the expression of genes involved in cell cycle control and apoptosis. Dysregulation of Estrogen Receptor Beta signaling may contribute to the increased risk of colorectal cancer, particularly in postmenopausal women [57].

2.6 Symptoms of Colon Cancer

Colon cancer often develops silently, especially in its early stages, which is why regular screening is critical. As the disease progresses, various symptoms may emerge, indicating the presence of cancer. Recognizing these symptoms early can significantly impact prognosis and treatment outcomes.

2.6.1 Changes in Bowel Habits

One of the earliest and most common symptoms of colon cancer is changes in bowel habits. Patients may experience diarrhea, which manifests as frequent loose stools often accompanied by an urgent need to defecate. This symptom can be intermittent or persistent, sometimes misattributed to other gastrointestinal issues like irritable bowel syndrome.

Conversely, some individuals may encounter prolonged periods of constipation, which can occur when a tumor obstructs the passage of stool through the colon. Additionally, patients may notice that their stools have changed in shape, becoming narrower or ribbon-like, which can indicate a narrowing of the colon due to a tumor [58].

2.6.2 Blood in Stool

Blood in the stool is a serious sign that should never be disregarded. Blood can appear in different forms; bright red blood typically suggests bleeding from the lower sections of the colon or rectum, while dark or tarry stools may indicate bleeding higher up in the gastrointestinal tract.

Bright red blood can be associated with conditions such as hemorrhoids, but it can also signal more serious issues, including colorectal cancer. Dark stools, on the other hand, suggest the presence of digested blood and require immediate medical evaluation, as they may indicate an advanced stage of the disease [59].

2.6.3 Abdominal Discomfort

Abdominal pain or discomfort is another significant symptom of colon cancer. Patients may experience cramping, which can be continuous or intermittent as the tumor disrupts normal bowel function. This discomfort is often localized to the lower abdomen, particularly if the tumor is located in the sigmoid colon or rectum. Bloating is also common, characterized by a feeling of fullness or swelling in the abdomen. This sensation can result from gas buildup and is often exacerbated by dietary factors or changes in bowel habits. Persistent or severe abdominal pain that does not improve may indicate an underlying issue, such as a tumor [60].

2.6.4 Unexplained Weight Loss

Unintentional weight loss is a concerning symptom that can be associated with many types of cancer, including colon cancer. Patients may find themselves losing weight without trying, which can be attributed to several factors. Decreased appetite is a common contributor, as cancer can affect appetite due to metabolic changes or psychological factors, leading individuals to feel less inclined to eat. Additionally, if the tumor obstructs the colon, it may result in malabsorption of nutrients, exacerbating weight loss. This symptom warrants attention, particularly when accompanied by other gastrointestinal signs [61].

2.6.5 Fatigue and Weakness

Fatigue is a prevalent symptom experienced by many cancer patients, including those with colon cancer. This fatigue may manifest as chronic tiredness or weakness that persists despite adequate rest. Patients often report feeling drained of energy, which can significantly impact their daily activities and overall quality of life. Chronic blood loss from the tumor can lead to anemia, further contributing to feelings of fatigue. A reduction in red blood cells causes anemia, which exacerbates the feeling of weariness by causing weakness and shortness of breath [62].

2.6.6 Tenesmus

Tenesmus is the sensation of incomplete evacuation after a bowel movement, accompanied by a persistent urge to defecate. This symptom can be particularly distressing for patients and may occur due to tumors located in the rectum, which can irritate the surrounding tissue.

The feeling of needing to go to the bathroom without producing significant stool can lead to frequent restroom visits. This uncomfortable sensation often causes anxiety and may affect a patient's social interactions and daily routines [63].

2.6.7 Additional Symptoms

While the previously mentioned symptoms are the most common, colon cancer can also present with additional signs. Nausea and vomiting may occur, particularly if the tumor causes a blockage in the colon, leading to a backup of intestinal contents. Changes in appetite are also common, as patients may experience a general decline in their desire to eat, often accompanied by weight loss.

Persistent low-grade fever may be present, especially if there is an associated infection or inflammation related to the tumor. These additional symptoms highlight the complex nature of colon cancer and the importance of comprehensive evaluation [60].

2.7 Treatments for Colon Cancer

Treatment for colon cancer is complex and usually includes a mix of immunotherapy, targeted treatments, radiation therapy, chemotherapy, and surgery. The location and size of the tumor, the patient's general health, the stage of the malignancy, and personal preferences all influence the treatment decision. Here's a detailed look at the primary treatment options available for colon cancer.

2.7.1 Surgery

For localized colon cancer, surgery is frequently the primary course of treatment and, if caught early, can be curative. The primary surgical technique is a colectomy, which involves the removal of the part of the colon containing the tumor along with a margin of healthy tissue. The location of the tumor determines the type of colectomy that is done.

A total colectomy, which is typically recommended for more advanced illness, entails removing the whole colon, whereas a partial colectomy eliminates the tumor along with a small amount of the surrounding healthy tissue. In some cases, particularly when reattachment is impossible, a colostomy may be performed, which creates an opening in the abdominal wall for waste to exit into a colostomy bag. During surgery, nearby lymph nodes are often removed and examined for cancer spread, aiding in determining the stage of cancer and guiding subsequent treatment decisions [64].

2.7.2 Chemotherapy

Chemotherapy employs drugs to kill cancer cells or slow their growth and is frequently used alongside surgery, especially when cancer has metastasized beyond the colon. Chemotherapy can be used as a neoadjuvant before surgery to reduce tumor size and facilitate removal, or as an adjuvant after surgery to eradicate any cancer cells that may still be present. Combinations like 5-Fluorouracil (5-FU), which is frequently used with leucovorin and oxaliplatin in a regimen known as FOLFOX, are common chemotherapy regimens for colon cancer. Another popular medicine is capecitabine, an oral prodrug that the body transforms into 5-FU.

Another choice is irinotecan, which is frequently combined with leucovorin and 5-FU in the FOLFIRI regimen. Although chemotherapy is successful, it can have negative side effects such as tiredness, nausea, vomiting, hair loss, and an increased risk of infection. However, improvements in supportive care have made it easier to manage these side effects [65].

2.7.3 Radiation Therapy

Although it is not usually the main treatment for colon cancer, radiation therapy, which utilizes high-energy rays to destroy cancer cells, can be helpful in some circumstances. While postoperative radiation can aid in the removal of any remaining cancer cells, particularly in cases where there is a significant risk of local recurrence, preoperative radiation may be used to reduce tumors prior to surgery, especially for rectal cancer. Palliative radiation therapy may be performed in more advanced situations to alleviate tumor-related symptoms including pain or blockage. Depending on the area being treated, radiation treatment side effects may include gastrointestinal distress, skin irritation, and exhaustion [66].

2.7.4 Targeted Therapy

The goal of targeted therapy is to minimize harm to healthy cells while precisely addressing the traits of cancer cells. Patients who have certain genetic alterations linked to their cancers may benefit most from these treatments. For example, EGFR inhibitors, such as cetuximab and panitumumab, are usually utilized in situations of metastases and target the epidermal growth factor receptor on cancer cells, although they are effective only in tumors that do not have mutations in the KRAS gene. Additionally, VEGF inhibitors, such as bevacizumab, prevent the formation of new blood vessels that tumors need to grow, often used in combination with chemotherapy for advanced colon cancer [67].

2.7.5 Immunotherapy

Immunotherapy harnesses the body's immune system to combat cancer. While its effectiveness in colon cancer has been limited compared to other cancers, specific subsets of colon cancer patients may benefit from this approach. Immune checkpoints like PD-1 are targeted by checkpoint inhibitors like pembrolizumab and nivolumab, which can be especially useful in patients with cancers that have a high level of microsatellite instability or that lack mismatch repair. Because of

the distinct features of their malignancies, these individuals usually have a better chance of responding to immunotherapy. Although they are still mostly experimental, research is being done on cancer vaccines that aim to activate the immune system to combat colon cancer cells [68].

2.7.6 Clinical Trials

By giving patients the chance to take part in studies evaluating new medications, combination treatments, or innovative techniques, clinical trials are essential to improving the treatment of colon cancer. These studies may provide access to innovative treatments that are not yet generally accessible and are crucial for assessing the safety and effectiveness of new therapeutic approaches.

2.8 Side Effects of Available Treatments

Although many treatments are available for colon cancer treatment but they have side effects associated with them, which are discussed below.

2.8.1 Pain at the Surgical Site

After surgery for colon cancer, patients often experience pain at the surgical site. This pain can vary in intensity and may require medication for relief. The discomfort may persist for several weeks as the body heals, and some patients may also experience referred pain in the abdomen or back [69].

2.8.2 Changes in Bowel Habits

Surgery and chemotherapy can lead to major changes in bowel habits. Constipation, diarrhea, or changes in stool consistency are possible side effects for patients. These changes can be temporary, but some individuals may face long-term bowel

dysfunction, particularly if a significant portion of the colon has been removed [58].

2.8.3 Nausea and Vomiting

Chemotherapy is commonly associated with nausea and vomiting, which can occur shortly after treatment or persist for several days. This side effect can severely affect a patient's standard of living and might result in dehydration or malnutrition if not managed effectively [70].

2.8.4 Fatigue

Fatigue is a prevalent side effect experienced by patients undergoing chemotherapy, radiation therapy, and immunotherapy. This overwhelming sense of tiredness can interfere with daily activities and may persist even after treatment has ended [71].

2.8.5 Hair Loss

One well-known adverse effect of many chemotherapy treatments is hair loss. Patients may suffer from total hair loss or thinning hair, which can be upsetting and have an impact on their self-esteem.

Hair typically begins to regrow after the completion of treatment, although it may change in texture or color [72].

2.8.6 Diarrhea

Diarrhea can occur as a side effect of chemotherapy, radiation therapy, and targeted therapies. It can lead to dehydration and electrolyte imbalances if not managed properly. Patients experiencing diarrhea may require dietary adjustments and medications to alleviate their symptoms [73].

2.8.7 Skin Rashes

Targeted therapies and immunotherapy can lead to skin rashes, which may manifest as redness, irritation, or acne-like lesions. Targeted therapies and immunotherapy can lead to skin rashes, which may manifest as redness, irritation, or acne-like lesions. These rashes can be uncomfortable and may require topical or systemic treatments to manage [74].

2.8.8 Peripheral Neuropathy

A common adverse effect of several chemotherapy medications, especially oxaliplatin, is peripheral neuropathy. Patients may suffer from discomfort, tingling, or numbness in their hands and feet, which can interfere with day-to-day tasks.

This side effect may improve after treatment ends, but some patients experience lingering symptoms [75].

2.8.9 Increased Risk of Infections

Chemotherapy can suppress bone marrow function, leading to a decreased production of white blood cells. This suppression increases the risk of infections, making patients more susceptible to illnesses. To control this risk during therapy, routine monitoring and preventative steps are crucial [76].

2.8.10 Immune-related Adverse Events

Immunotherapy can trigger immune-related adverse events, where the immune system attacks healthy organs and tissues.

Common issues include colitis, pneumonitis, and hepatitis. These side effects can be serious and require prompt medical intervention to manage effectively [77].

2.8.11 Fatigue from Radiation Therapy

Patients undergoing radiation therapy often experience fatigue that can accumulate over the course of treatment. This fatigue can last for weeks or even months after completing therapy, impacting overall well-being and daily functioning [78].

2.8.12 Long-term Bowel Dysfunction

Long-term bowel dysfunction can result from surgery or radiation therapy, leading to issues such as incontinence, urgency, or strictures. These complications can significantly affect a patient's quality of life and may require ongoing management [79].

2.8.13 Constipation

Constipation can occur as a side effect of surgery, chemotherapy, and certain pain medications. Patients may experience infrequent bowel movements, straining, and discomfort. Dietary changes, increased fluid intake, and medications may be necessary to manage this condition effectively [80].

2.8.14 Dehydration

Side effects including nausea, vomiting, and diarrhea can cause dehydration, especially during chemotherapy and radiation treatment. It can lead to symptoms like dry mouth, dizziness, and fatigue. Maintaining hydration through fluids and electrolytes is crucial, especially during treatment [81].

2.8.15 Mouth Sores

Chemotherapy can lead to mucositis, which manifests as painful sores in the mouth. These sores can make eating and swallowing difficult and may increase

the risk of infections. Good oral hygiene and topical treatments can help manage this side effect [82].

2.8.16 Changes in Appetite

Many patients undergoing chemotherapy experience changes in appetite, which can lead to weight loss or malnutrition. Taste alterations and nausea can contribute to decreased food intake. Nutrition counseling and appetite stimulants may be helpful in addressing these changes [83].

2.8.17 Liver Function Abnormalities

Targeted therapies, particularly those that affect the liver, can lead to elevated liver enzymes and other abnormalities. Monitoring liver function tests during treatment is essential, as significant changes may require dose adjustments or discontinuation of therapy [84].

2.8.18 Infusion Reactions

Some patients may experience infusion reactions during chemotherapy or targeted therapy administration, leading to symptoms such as fever, chills, rash, or difficulty breathing. These reactions can often be managed with premedication and close monitoring during infusions [85].

2.8.19 Fluid Retention

Certain targeted therapies and corticosteroids used for managing side effects can cause fluid retention, leading to swelling in the legs, abdomen, or face. This side effect may require dietary adjustments and diuretics to manage effectively [86].

2.8.20 Cognitive Changes

Some patients report cognitive changes, often referred to as "chemo brain," which may include difficulties with concentration, memory, and mental clarity during and after chemotherapy. These changes can affect daily functioning and may persist for some time post-treatment [87].

2.8.21 Hormonal Changes

Immunotherapy and certain targeted therapies can lead to hormonal changes, particularly if they affect the endocrine system.

Patients may experience symptoms such as weight gain, mood swings, or changes in libido, requiring careful management [88].

2.8.22 Hot Flashes

Patients undergoing certain treatments may experience hot flashes as a side effect. Patients undergoing certain treatments may experience hot flashes as a side effect.

This is particularly common in those receiving hormonal therapies or immunotherapies that affect hormone levels, leading to discomfort and interruptions in daily activities [89].

2.8.23 Secondary Cancers

While rare, some patients may develop secondary cancers as a long-term consequence of chemotherapy or radiation therapy. Ongoing monitoring and screenings are essential to detect any new malignancies early [90].

2.9 Herbal Treatments for Colon Cancer: Potential Benefits and Bioactive Metabolites

Conventional therapies including radiation therapy, chemotherapy, and surgery are important in the management of colon cancer, but they have serious adverse effects. Colon cancer is a major global health problem. There is growing interest in complementary therapies, particularly from herbal sources. Many plants contain bioactive metabolites that may offer protective or therapeutic effects against colon cancer. Several herbs and their active compounds have been explored that have shown promise in this area as shown in figure 2.4.

Turmeric (Curcuma longa) is perhaps one of the most studied herbs in relation to cancer treatment. Its primary active component, curcumin, has garnered attention because to its potent anti-inflammatory and antioxidant properties. It has been shown that curcumin slows the development of tumors by altering many signaling pathways linked to the onset of cancer, cause apoptosis, or programmed cell death, and prevent the growth of colon cancer cells. Curcumin is a useful adjuvant treatment since preclinical research has shown that it can also increase the efficacy of traditional chemotherapy drugs. Its capacity to enhance the gastrointestinal tract's general health emphasizes its importance in the treatment of colon cancer [91].

FIGURE 2.4: Herbal treatments for colon cancer

Green tea (*Camellia sinensis*) is another herbal remedy that has been linked to cancer prevention, particularly due to its high concentration of catechins, with epigallocatechin gallate (EGCG) being the most prominent. Numerous studies have shown that EGCG has strong anticancer effects, including the capacity to stop colon cancer cells from growing and lessen metastasis. Its antioxidant properties may help protect cells from oxidative damage, which is a contributing factor in cancer development. Regular consumption of green tea has been associated with a lower risk of developing colon cancer, making it a simple yet effective addition to a cancer-preventive diet [92]. Ginger (*Zingiber officinale*), widely recognized for its culinary uses, also holds therapeutic potential in cancer treatment. Gingerol, the primary ingredient, has anti-inflammatory and anti-cancer qualities. According to research, ginger extracts can help lower gastrointestinal tract inflammation and stop the development of colon cancer cells, which is especially advantageous for patients receiving chemotherapy. Ginger may help patients' quality of life during treatment by reducing nausea, a sometimes crippling adverse effect of chemotherapy [93].

Milk thistle (*Silybum marianum*) is renowned for its liver-protective properties, primarily due to its active compound, silymarin. Cancer patients may benefit from the antioxidant and anti-inflammatory properties of this flavonoid compound. According to studies, silymarin can help in functioning of liver and prevent colon cancer cells from proliferating, which would help with detoxification during cancer therapy. Milk thistle may help lessen some of the negative side effects of traditional treatments by promoting liver function [94]. Aloe vera (*Aloe barbadensis miller*) is another herb that has shown potential in cancer management. Aloin and aceman-nan, two substances found in aloe vera gel and juice, have anti-inflammatory and immunomodulatory properties. Aloe vera may improve the immune system and slow the growth of tumors in colon cancer patients, according to some research. It is a helpful supplement to cancer treatment because of its calming qualities, which can also reduce gastrointestinal pain [95].

Broccoli (*Brassica oleracea*) and other cruciferous vegetables are rich in glucosinolates, which are converted into bioactive compounds like sulforaphane during

digestion. The anticancer properties of sulforaphane, especially in colon cancer, have been well investigated. According to research, sulforaphane may lower the risk of cancer by enhancing detoxifying enzymes, causing apoptosis, and inhibiting the formation of cancer cells. Broccoli and other similar vegetables may help prevent colon cancer if consumed regularly [96]. The well-known adaptogen ginseng (*Panax ginseng*) has being investigated for possible anticancer effects. The active ingredients, called ginsenosides, have a number of biological properties, such as apoptosis induction and colon cancer cell growth suppression. Ginseng may also enhance the effectiveness of chemotherapy, making it a worthy consideration for patients seeking complementary therapies. Furthermore, its immune-enhancing effects can help support overall health during cancer treatment [97].

Lignans, which are abundant in flaxseed (*Linum usitatissimum*), have been linked to anticancer properties. Flaxseed is a good addition to a diet that fights cancer since studies have shown that it may help limit tumor development and enhance intestinal health. Additionally, its high fiber content helps support regular bowel motions and digestive health, which is especially crucial for individuals with colon cancer [98]. Another substance being researched for its potential anticancer effects is resveratrol, which is present in red wine and grapes. It has been demonstrated to cause apoptosis and stop colon cancer cells from growing. Resveratrol's ability to modulate various signaling pathways involved in cancer progression makes it a compelling subject of ongoing research, and it may offer additional benefits when combined with conventional treatments [99]. Neem (*Azadirachta indica*) has a long history of use in traditional medicine. The active compound azadirachtin exhibits anticancer properties by inhibiting cell proliferation and inducing apoptosis in cancer cells. Neem's potential to support immune function further emphasizes its role in holistic cancer care [100].

2.10 *Prunus armeniaca*

Prunus armeniaca (apricot) are small, orange-colored fruits belonging to the Rosaceae family. They are native to Armenia and have been cultivated for thousands

of years, spreading across various regions, including the Mediterranean, Central Asia, and eventually to Europe and the Americas. Apricots are valued for their nutritional and therapeutic qualities in addition to their sweet and tart flavor. Apricots, which are high in vitamins, minerals, and bioactive substances, have been shown to offer possible health advantages, such as helping to prevent and cure cancer [101].

FIGURE 2.5: Apricot plant morphology

2.10.1 Morphology and Taxonomy

The apricot tree is a deciduous species that typically reaches heights of 8 to 12 meters. Its structure is characterized by a rounded canopy, which becomes lush with foliage during the growing season as shown in figure 2.5. The branches are often thick and slightly twisted, providing a sturdy framework for the tree. In early spring, apricot trees produce fragrant white to pink flowers that bloom before the leaves emerge. These blossoms are not only beautiful but also attract a variety of pollinators, including bees, which are essential for fruit set. The leaves of the apricot tree are broad, ovate, and serrated, measuring about 5 to 10 centimeters in length. They display a vibrant green color in the summer, contributing to the tree's aesthetic appeal. The leaf arrangement is alternate, with each leaf attached to the stem by a short petiole. The foliage plays a critical role in photosynthesis, allowing the tree to produce the energy needed for fruit development [102].

The fruit itself is classified as a drupe, which is a type of fruit characterized by a hard stone or pit that encloses the seed. Apricots have a smooth skin that can range in color from pale yellow to deep orange, depending on the variety and ripeness. The flesh of the apricot is juicy and sweet, with a slightly tart undertone. Because of their rich flavor, apricots are popular both when eaten raw and in a range of culinary preparations, such as jams, jellies, and desserts. Apricots are typically harvested in late spring to early summer, with the timing dependent on the climate and specific cultivar. The harvesting process requires careful handling to avoid bruising the delicate fruit. Once harvested, apricots can be consumed fresh or processed into various products, such as dried apricots, which have a concentrated flavor and longer shelf life. Taxonomically, apricots belong to the genus Prunus, which includes other stone fruits like cherries, plums, and peaches [103]. This genus is part of the Rosaceae family, which is known for its diverse range of fruit-bearing plants. The scientific classification of apricots is as follows.

Kingdom	Plantae
Division	Angiosperms
Class	Eudicots
Order	Rosales
Family	Rosaceae
Genus	*Prunus*
Species	*P. armeniaca*

The genus Prunus is further divided into several sections, with apricots classified under the section Prunus. This section also includes other economically important fruits. Within the species P. armeniaca, there are numerous cultivars and varieties, each differing in size, color, flavor, and adaptability to various climates. Some of the most well-known apricot varieties include 'Katy,' 'Tilton,' and 'Blenheim,' each prized for its unique flavor profile and culinary uses. Apricot trees thrive in well-drained soils and prefer a climate with warm summers and cold winters. They require a certain number of chilling hours for proper fruit development, making them suitable for temperate regions. The trees are sensitive to late frosts, which can damage blossoms and significantly reduce fruit yield. As a result, careful

consideration of planting location and climate is essential for successful apricot cultivation [104].

2.10.2 Traditional and Ethnomedical Uses of Apricot

Historically, apricots have held a significant place in the traditional medicine practices of various cultures. The fruit's origins can be traced back to ancient Armenia, where it was recognized for its nutritional and medicinal properties. Ancient Egyptians recognized the healing potential of apricots and utilized them to treat digestive issues, often consuming them to alleviate constipation and promote overall digestive health. They believed that the fruit's high fiber content could aid in maintaining a healthy gut. In traditional chinese medicine, apricots, particularly the seeds, were employed to promote lung health and alleviate respiratory conditions. The seeds, known as "bitter almonds," were used for their expectorant properties, helping to relieve coughs and respiratory ailments. Traditional chinese medicine practitioners valued apricots for their ability to nourish the lungs and improve overall respiratory function, making them a staple in herbal formulations aimed at treating coughs and colds [105].

In addition to digestive and respiratory health, apricots have been used in various folk remedies. In some cultures, the fruit was believed to have cooling properties that could help relieve fevers and inflammation. Apricot leaves and flowers were sometimes brewed into teas or used in poultices to manage skin irritations and promote healing. This historical use of apricots underscores their longstanding role in traditional medicine, reflecting the fruit's versatility and therapeutic potential [106].

The ethnomedical uses of apricots extend beyond their nutritional value. The fruit and its components have been utilized to treat a multitude of health conditions. The rich content of vitamins A and C in apricots contributes to their reputation for promoting skin health and improving vision. Vitamin A is essential for maintaining healthy skin and eyes, while vitamin C plays a critical role in collagen synthesis and acts as a powerful antioxidant. Apricots are also known for their ability to alleviate

digestive disorders, such as constipation and indigestion, due to their high fiber content. Apricots are also known for their ability to alleviate digestive disorders, such as constipation and indigestion, due to their high fiber content. The fruit has been traditionally used for its laxative properties, helping to promote regular bowel movements and support gastrointestinal health [107].

Apricot kernels, which contain amygdalin, have been controversially promoted as a treatment for cancer. While some proponents claim that amygdalin can inhibit tumor growth, scientific support for this assertion is limited, and caution is advised due to potential toxicity. Because of its purported capacity to improve respiratory health and alleviate coughs, the kernels are occasionally utilized in traditional medicine.

However, due to the presence of cyanogenic compounds in the seeds, which can release toxic cyanide when metabolized, consumers must approach this treatment with caution and seek guidance from healthcare professionals. Moreover, apricot extracts have been used in skincare products for their moisturizing and healing properties. The antioxidants in apricots can help protect the skin from oxidative damage caused by environmental factors, promoting a healthy complexion.

In some cultures, apricot oil derived from the seeds is used for massage and skin treatments, highlighting the fruit's versatility beyond dietary applications [31].

2.10.3 Bioactive Compounds in Apricots

Apricots are rich in bioactive compounds, as shown in figure 2.6. These compounds contribute to their potential health benefits, particularly in the context of cancer prevention and treatment.

These compounds play critical roles in combating oxidative stress and inflammation, both of which are key factors in cancer development. Several key bioactive compounds found in apricots, emphasizing their anticancer properties, are discussed below.

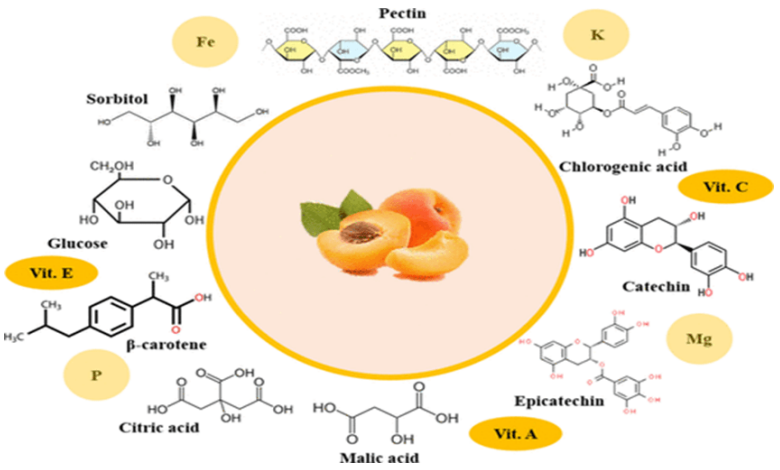


FIGURE 2.6: Bioactive compounds in apricot

2.10.3.1 Quercetin

Quercetin is one of the most notable flavonoids present in apricots, renowned for its powerful antioxidant and anti-inflammatory properties. This compound has been shown to inhibit the growth of cancer cells and induce apoptosis, making it a significant player in cancer prevention strategies.

By scavenging free radicals, quercetin helps reduce oxidative stress, which can damage cellular structures and lead to cancer progression. In studies focused on cancer, quercetin has demonstrated the ability to inhibit tumor growth and enhance the efficacy of conventional chemotherapy agents. Its multifaceted action makes quercetin a valuable compound in the fight against colon cancer [108].

2.10.3.2 Hyperoside

Hyperoside, a glycoside of quercetin, shares many of its parent compound's beneficial properties. Research indicates that hyperoside may enhance the anticancer effects of quercetin. It has been found to modulate various signaling pathways involved in cell proliferation and apoptosis, reinforcing its potential role as a preventive agent against cancer. Hyperoside's ability to reduce inflammation also contributes to its effectiveness in supporting colon health, making it a promising compound for further exploration in cancer therapies [109].

2.10.3.3 Kaempferol

Another flavonoid found in apricots, kaempferol has demonstrated significant anticancer properties. Studies indicate that kaempferol can inhibit the proliferation of cancer cells and induce apoptosis. Its anti-inflammatory effects are crucial in preventing cancer development, as chronic inflammation is often linked to tumor formation. By reducing inflammation and supporting cellular health, kaempferol presents a compelling argument for its inclusion in a diet aimed at cancer prevention [110].

2.10.3.4 Caffeic Acid

Caffeic acid is a phenolic compound known for its antioxidant and anti-inflammatory properties. Research shows that caffeic acid can inhibit the growth of cancer cells, including those in the colon. Its ability to enhance the efficacy of other anticancer agents makes it a valuable component in treatment strategies. Caffeic acid strengthens apricots' anti-cancer properties by shielding cells from oxidative stress and inflammation [110].

2.10.3.5 Limonene

The terpene limonene, which is present in the essential oils of many fruits, has anti-inflammatory and anti-cancer effects. According to studies, limonene may improve the body's immunological response against cancer and slow the growth of tumors, potentially improving patient outcomes. Its presence in apricots adds another layer of complexity to the fruit's cancer-fighting potential [111].

2.10.3.6 Catechins

Catechins are a class of flavonoids with strong antioxidant properties that have been shown to inhibit cancer cell growth and promote apoptosis. Their presence in apricots contributes to the fruit's overall anticancer potential, making them

valuable components in a health-promoting diet. Catechins help combat oxidative stress in the body, thereby supporting cellular integrity and reducing cancer risk [112].

2.10.3.7 Geraniol

Another terpene that has been shown to have anti-inflammatory and anti-cancer effects is geraniol, which is present in apricots.

According to research, geraniol can improve the efficacy of traditional cancer therapies by preventing the growth of cancer cells. Its function in lowering inflammation and boosting immunity offers a thorough method of treating cancer [113].

2.10.3.8 Folate

Folate, also referred to as vitamin B9, is necessary for the creation and repair of DNA. Consuming enough folate has been associated with a lower chance of developing several types of cancer, such as colon cancer.

The fruit's ability to promote cellular health and lower the risk of cancer is highlighted by the folate found in apricots. Folate aids in preventing cancer-causing mutations by encouraging healthy DNA synthesis [114].

2.10.3.9 Cyanidin

Cyanidin, a type of anthocyanin responsible for the deep color in many fruits, possesses strong antioxidant properties. According to studies, cyanidin may lessen inflammation and stop the growth of cancer cells, further contributing to apricots' health benefits. According to studies, cyanidin may lessen inflammation and stop the growth of cancer cells, further contributing to apricots' health benefits. Its ability to combat oxidative stress makes cyanidin a noteworthy compound for cancer prevention [115].

2.10.3.10 Chlorogenic Acid

The anti-inflammatory and antioxidant properties of chlorogenic acid are well-known. According to research, chlorogenic acid can lower the risk of cancer by preventing the formation of cancer cells and fostering normal cellular processes. In the battle against cancer, chlorogenic acid provides another layer of synergy by enhancing the preventive benefits of apricots [116].

2.10.3.11 Beta-carotene

Beta-carotene, a carotenoid that is converted into vitamin A in the body. Beta-carotene is well-known for its antioxidant properties, which help protect cells from oxidative damage caused by free radicals. This preventive effect is essential for lowering the risk of several types of cancer. Beta-carotene is a vital ally in the fight against cancer because it preserves the integrity of cellular structures and encourages healthy cell activity [117].

2.10.3.12 Vitamin E

This fat-soluble vitamin is recognized for its strong antioxidant properties, helping to safeguard cell membranes from oxidative stress. Research indicates that consuming enough vitamin E may lower your chance of developing several types of cancer, including colon cancer. Its role in protecting cells from damage and promoting overall health makes vitamin E a vital component of a cancer-preventive diet [118].

2.10.3.13 Magnesium

Magnesium is another essential mineral present in apricots that plays a critical role in numerous biochemical reactions in the body. It is particularly important for DNA repair and synthesis, processes that are vital for maintaining cellular health. Adequate magnesium levels have been linked to a lower risk of certain

cancers, including colon cancer, as it supports healthy cell division and function. This mineral's involvement in DNA maintenance underscores the importance of apricots as a source of nutrients that contribute to overall cellular integrity and cancer prevention [118].

2.10.3.14 Dietary Fibers

In addition to the above compounds, apricots contain a variety of dietary fibers, which not only aid in digestion but also play a role in reducing the risk of colorectal cancer. Fiber helps to promote regular bowel movements and may assist in the elimination of potential carcinogens from the gut, thereby lowering the risk of cancer development in the colon [119].

2.10.3.15 Medical Uses of Apricot

Apricots have a long history of use in traditional medicine, and modern research continues to explore their potential therapeutic applications as shown in figure 2.7. Some notable medical uses of apricots are discussed below.

2.10.3.16 Digestive Health

Apricots are rich in dietary fiber, which promotes healthy digestion and regular bowel movements. The high fiber content helps alleviate constipation and supports overall gastrointestinal health. Consuming apricots can aid in maintaining a healthy gut microbiome, which is crucial for nutrient absorption and digestive efficiency [16].

2.10.3.17 Antioxidant Properties

The bioactive substances found in apricots, including quercetin, vitamin C, and beta-carotene, possess strong antioxidant properties. These antioxidants help combat oxidative stress in the body, reducing the risk of chronic diseases, including

cancer. By neutralizing free radicals, apricots may protect cells from damage and support overall health [120].

2.10.3.18 Skin Health

Apricots are well known for their capacity to improve the health of the skin. The vitamins A and E present in apricots help maintain skin integrity and promote healing. Apricot oil, derived from the seeds, is often used in cosmetics and skincare products for its moisturizing and nourishing properties.

The vitamins A and E present in apricots help maintain skin integrity and promote healing. Apricot oil, derived from the seeds, is often used in cosmetics and skincare products for its moisturizing and nourishing properties. It may help improve skin elasticity and reduce signs of aging [121].

2.10.3.19 Vision Support

The high levels of beta-carotene in apricots can contribute to improved vision health. Beta-carotene is converted into vitamin A in the body, which is essential for maintaining good eyesight and preventing night blindness.

Regular consumption of apricots may help protect against age-related macular degeneration and other vision-related issues [101].

2.10.3.20 Weight Management

With their low calorie and high fiber content, apricots can be a beneficial addition to a weight management plan. The fiber helps promote feelings of fullness, which may aid in reducing overall calorie intake. Including apricots in a balanced diet can support healthy weight loss and maintenance [122].

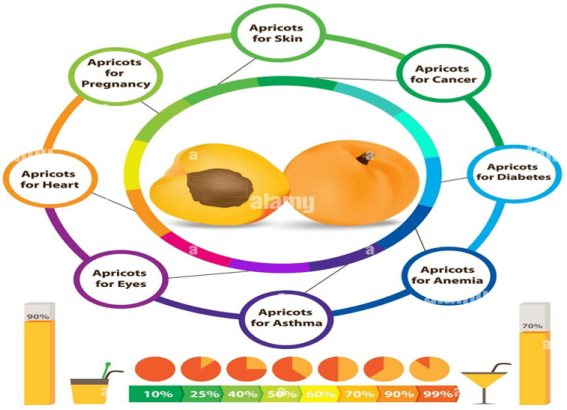


FIGURE 2.7: Medical uses of apricot

2.10.3.21 Heart Health

Apricots contain potassium, which is essential for maintaining healthy blood pressure levels. Potassium helps counteract the effects of sodium and supports proper heart function. Additionally, the antioxidants in apricots may help reduce inflammation and oxidative stress in the cardiovascular system, contributing to overall heart health [16].

2.10.3.22 Cancer Prevention

The possible anticancer effects of the bioactive substances in apricots, especially flavonoids and phenolic acids, have been investigated. According to research, these substances may cause apoptosis and stop the development of cancer cells, particularly those in the colon. The anti-inflammatory effects of apricots also play a role in reducing cancer risk [11].

2.10.3.23 Respiratory Health

In traditional medicine, apricot seeds have been used for their expectorant properties, helping to relieve coughs and support respiratory health. While caution is advised due to potential toxicity from amygdalin in the seeds, the fruit itself can promote lung health due to its overall nutrient profile [16].

2.10.3.24 Boosting Immunity

The vitamins and antioxidants in apricots help strengthen the immune system. Vitamin C, in particular, is known for its role in enhancing immune function, helping the body defend against infections and diseases. Regular consumption of apricots may contribute to improved immune response [123].

2.10.3.25 Blood Sugar Regulation

Some research suggests that apricots may help regulate blood sugar levels due to their low glycemic index and high fiber content. The fiber slows the absorption of sugar, helping to prevent spikes in blood glucose levels. This makes apricots a suitable fruit option for individuals with diabetes or those looking to manage their blood sugar levels [124].

Although Prunus armeniaca shows promising potential in managing medical problems, further research is needed to explicitly link its effects to the specific proteins associated with colon cancer. The existing studies primarily focus on broader health outcomes rather than direct interactions with the target proteins. The present study aims to identify possible anti-cancerous phytocompounds from the Prunus armeniaca plant for healthy colon functioning.

Chapter 3

Methodology

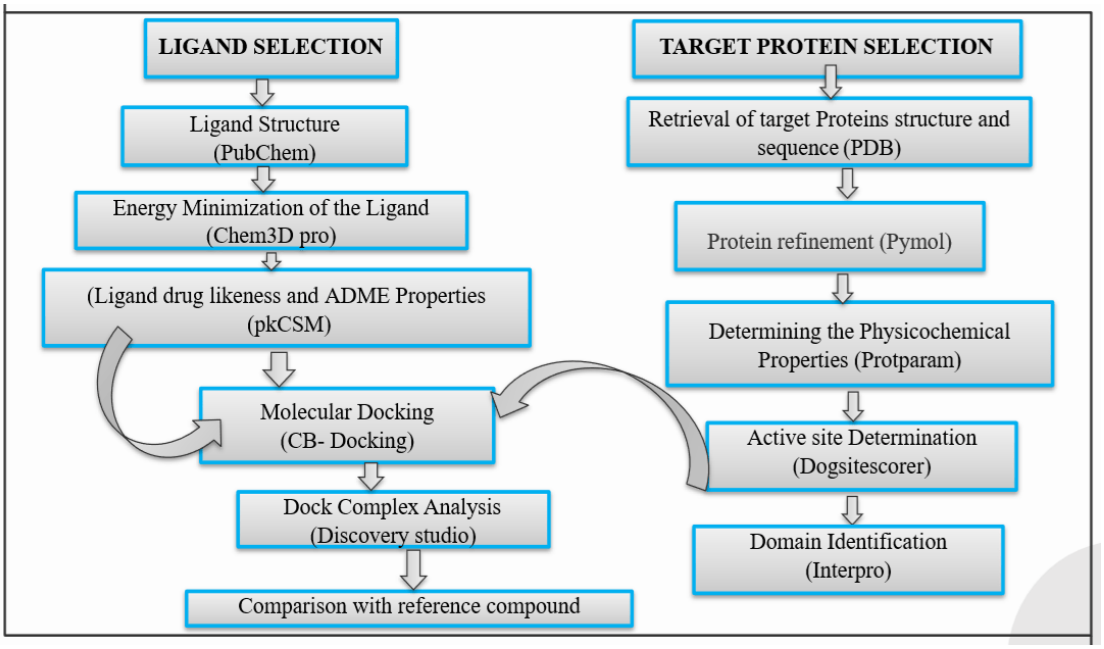


FIGURE 3.1: The Methodology Flowchart

3.1 Selection of Problem

A complicated medical condition, colon cancer is impacted by environmental factors, genetic predispositions, and lifestyle decisions. Alternative therapies can sometimes lead to unintended physiological consequences, making safer and more effective strategies crucial. Proteins like carbonic anhydrase, aldose reductase and estrogen receptor beta have emerged as important targets in understanding colon

cancer mechanisms. Investigating these proteins could lead to novel treatments and improved patient outcomes [125].

3.2 Selection of Target Proteins

The selection of specific proteins in colon cancer research focuses on their critical roles in regulating cell differentiation, signaling pathways, and metabolic processes. Carbonic anhydrase 9 (CA9), aldose reductase (AR), and estrogen receptor beta (ERB) were chosen for their significant contributions to tumor biology. Carbonic anhydrase 9 is pivotal in the adaptation of cancer cells to hypoxic environments, facilitating tumor growth. Aldose reductase participates in metabolic processes that affect the survival and growth of cells, while estrogen receptor beta plays a complex role in modulating cellular responses to estrogen, which can affect cancer progression. Together, these proteins represent essential targets for understanding and potentially managing colon cancer [126].

3.3 Target Proteins FASTA Sequence Retrieval & Structure Prediction

The 3D structures can be predicted through PDB (https://www.rcsb.org/) [127]. Alternatively, I-TASSER can be used if some structures are not available on PDB. I-TASSER (https://zhanglab.ccmb.med.umich.edu/I-TASSER/) stands for Interactive Threading Assembly Refinement. This software is available online and it predicts the three-dimensional structure and function of proteins. First of all, it identifies the structural model of the PDB through various strategies which include the atomic models of full length and they are built by using simulations of the different threading fragments [55]. The 3D structure of proteins is also predicted by the I-TASSER service and this server gives us five 3D structures of proteins so based on C-score we can select the best 3D structure of the protein [128]. Alphafold (https://alphafold.com/) is another reliable source for the prediction of

the 3D structure of proteins [129]. The FASTA sequence of the selected the protein sequence database provided the target proteins. PDB. Alternatively, Uniprot (http://www.uniprot.org/) or NCBI (https://www.ncbi.nlm.nih.gov/) databases can also be used for sequence retrieval of target proteins [130].

3.4 Target Proteins Physicochemical Properties Analysis

The function of the proteins is significantly influenced by their physicochemical characteristics. ProtParam expasy tool (https://web.expasy.org/protparam/) was used for the prediction of these features of carbonic anhydrase 9, aldose reductase and estrogen receptor beta. ProtParam was used to calculate the number of negatively charged residues (Asp+ Glu) and positively charged residues (Arg+ Lys), theoretical pI, molecular weight, aliphatic index, grand average of hydrophobicity, instability index, Ext coefficient (with Cys) and Ext coefficient (excluding Cys [131]).

3.5 Protein Structure Analysis and Refinement by Use of PyMol

PyMOL (https://pymol.org/) is an open-source molecular graphics application that has been widely used all over the world to examine and portray various proteins and tiny chemicals in three dimensions including nucleic acids, densities of different electrons and varying surfaces, and also the trajectories. It is also used for editing the molecules, tracing the ray, and also to make animations and movies. This is software that is based on Python and also contains many plugin tools to enhance its use and facilitate drug targeting and designing by the use of PyMol software. The excess components linked to the protein must be deleted after downloading the protein structure which was done by the use of an open-source system PyMol [132].

3.6 Functional Domain Identification of Targeted Proteins

Interpro (http://www.interpro.com/) is a database that was utilized to determine the targeted proteins carbonic anhydrase 9, aldose reductase and estrogen receptor beta's functional domains. Sequence, structure, and relationships are all involved in conserved domains [133].

3.7 Active Site Identification

The area in which the target protein's active site is located is where the ligand exhibits the greatest or maximal interaction with the protein. Amino acids have a major role in the ligand-protein complex building process. Dogsitescorer (https://proteins.plus/help/dogsite) software was used for the detection of protein binding pockets [134].

3.8 Selection of Active Metabolic Ligands

After an extensive literature review, those ligands were selected that have previously shown some anticancer properties. These include quercetin, hyperoside, kaempferol, caffeic acid, limonene, catechins, geraniol, folate, cyanidin and chlorogenic acid [135].

3.9 Retrieval of Chemical Structure of Ligands

PubChem (https://pubchem.ncbi.nlm.nih.gov/) is the world's largest repository of easily accessible chemical information databases. So the chemical compounds that were selected as potential ligands were taken from the PubChem database in SDF format [136]. If in case the selected ligand structure is not available then our

next attempt would be to download the canonical smiles from PubChem and then insert them in the software Chem Draw to obtaining the 3D structure [137].

3.10 Energy Minimization of Ligands

Ligands energy was minimized by using Chem3D ultra. It is a necessary step to refine the ligands before performing docking otherwise, there will be unreliable docking scores [138].

3.11 Virtual Screening of Ligands by Application of Lipinski Rule of Five

An essential criterion for determining whether ligands are likely to be drugs is the Lipinski rule. Certain chemicals are likely to be utilized as active pharmaceuticals in humans if they adhere to the lipinski rule of five. pkCSM (https://omictools.com/pkcsm-tool) is an online tool that helps to check whether ligands obey lipinski rule or not [139]. The rules are described as under:

1. The log P value should be in the range of five.
2. Maximum number of H-bond acceptor should be limited to ten.
3. Maximum number of H-bond donor should be limited to five.
4. The molecular weight should be below five hundred grams.
5. Rotatable bonds should be limited to five.

3.12 Ligands ADMET Analysis

After filtering the ligands by applying the lipinski rule, the next step of the study was the prediction of pharmacokinetic and toxicity properties. pkCSM

(https://omictools.com/pkcsm-tool) was used for the prediction of the pharmacokinetic properties of selected ligands. The weak candidates of the drug would be eliminated during ADMET analysis. The remaining candidates can be selected as potential drugs against the disease. The target proteins were used to optimize the ADMET properties associated with the human body [140].

3.13 Molecular Docking

For performing the molecular docking between the protein and the ligand, CB-dock (Cavity detection guided blind docking) was used. CB-dock (http://clab.labshare.cn/cbdock/php/blinddock.php) finds the sites of docking automatically. CB-Dock is a method of protein and ligand docking that indicates the sites of bonding, the size, and the center calculated. The box size is adjusted according to the ligand and then docking is performed. The docking is performed through AutoDock Vina. Its accuracy ratio is greater because the docking process is more focused on cavity binding [141]. We uploaded the proteins to do docking, use the 3D structure in pdb format and the ligand's 3D structure in SDF format. After this docking is performed, the result would be 5 different poses of interaction. To select the best pose, we would look at the lowest docking score which is given in KJ/m^{-1} CB-Dock will provide an interactive 3D visualization of results in 5 different poses. Based on the lowest vina score expressed in (kJ/m1), the optimal position was chosen [142].

3.14 Analysis of Docked Complexes via Discovery Studio

To interpret docking findings, the interaction between the ligand and the protein's active pockets was calculated. Different types of interactions were examined including hydrophobic and hydrogen bonding. Discovery studio 2025 Client was used to analyze the protein-ligand interactions. The protein-ligand interactions for the

designated ligands in the PDB file are automatically schematically diagrammed by this application [143].

3.15 Lead Compound Identification

The most active inhibitor was found after a thorough examination of docking scores, pharmacokinetic studies, toxicity features, and protein and ligand interactions. Our lead compound was the one that followed all these parameters.

3.16 Reference Anti-cancer Drug Selection

The purpose of this step is to identify the commercial drugs that are already in use for anticancer disease treatment purposes. Drug Bank (https://go.drugbank.com/) database was used for this purpose because it provides details about drugs and their pathways [144].

3.17 Comparison between Lead Compound and Reference Drug

Docking values, molecular interactions, and pharmacokinetic features were compared between the reference anti-cancer drug and the suggested lead molecule.

Chapter 4

Results

4.1 3D Structure Prediction and Refinement of Selected Proteins

3D structures of target proteins carbonic anhydrase 9, aldose reductase and estrogen receptor beta were taken from PDB under pdb IDs 8Q1A, 1ABN and 1I2J respectively. Using PyMol, the protein structures were refined by eliminating any ligands and water molecules. To obtain stable conformation the absent polar hydrogens were added, and other atoms were removed to prevent overlaps and modified file was saved in PDB format. The refined structures of target proteins are shown in figure 4.1 below.

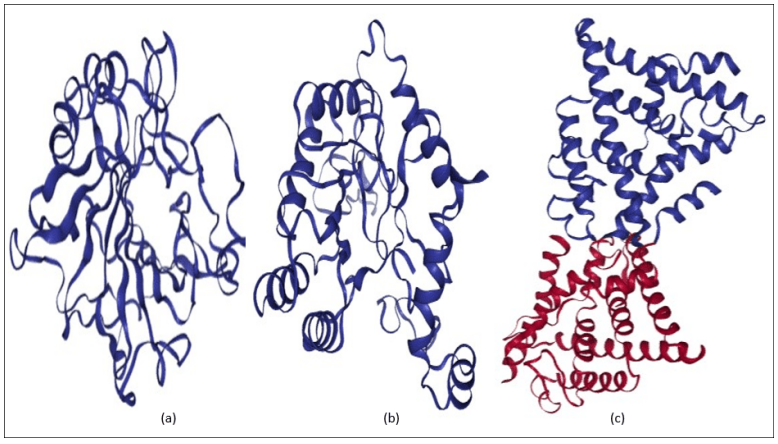


FIGURE 4.1: Structures of refined target proteins (a) Carbonic anhydrase 9 (b) Aldose reductase (c) Estrogen receptor beta

4.2 Primary Sequence Retrieval

FASTA sequences were obtained by using PDB. The FASTA sequence of carbonic anhydrase 9, aldose reductase and estrogen receptor beta was downloaded from PDB under IDs 8Q1A, 1ABN and 1I2J as shown in figure 4.2.

>8Q1A_1|Chains A| Carbonic anhydrase 9|Homo sapiens (9606)
GPDQSHWRYGGDPPWPRVSPACAGRFQSPVDIRPQLAAFSPALRPLELLGFQLPPLPELRLRNNGHSVQLTLPPGLEMALGPGREYRALQLHL
HWGAAGRPGSEHTVEGHRFPAEIHVVHLSTAFARVDEALGRPGGLAVLAAFLEEGPEENSAYEQLLSRLEEIAEEGSETQVPGLDISALLPSDFSR
YFQYEGSLTTPPCAQGVIWTVFQQTVMLSAKQLHTLSDTLWGPGDSRLQLNFRATQPLNGRVIEASFP
>1ABN_1|Chain A|ALDOSE REDUCTASE |Homo sapiens (9606)
ASRLLLNNGAKMPILGLGTWKSPPGQVTEAVKVAIDVGYRHIDCAHVYQNENEVGVAIQEKLREQVVKREELFIVSKLWCTYHEKGLVKGACQK
TLSDLKLDYLDLYLIHWPTGFKPGKEFFPLDESGNVVPSDTNILDTWAAMEELVDEGLVKAIGISNFNHLQVEMILNKPGLKYKPAVNQIECHPYL
TQEKLIQYCQSKGIVVTAYSPLGSPDRPWAKPEDPSLLEDPRIKAIAAKHNKTTAQVLIRFPMQRNLVVIPKSVTPERIAENFKVFDFELSSQDMTT
LLSYNRNWRVSALLSCTSHKDYPFHEEF
>1L2J_1|Chains A, B|ESTROGEN RECEPTOR BETA| Homo sapiens (9606)
MGSSHHHHHHSSGLVPRGSHMRELLLDALSPEQLVLTLLEAEPPHVLISRPSAPFTEASMMMSLTKLADKELVHMISWAKKIPGFVELSLFDQ
VRLLESCWMEVLMMGLMWRSIDHPGKLIFAPDLVLDRDEGKCVEGILEIFDMLLATTSRFRELKLQHKEYLCVKAMILLNSSMYPLVTATQD
ADSSRKLAHLLNAVTDALVWVIAKSGISSQQQSMRLANLLMLLSHVRHASNKGMEHLLNMKCKNVVPVYDLLLEMLNAHVLRGCKS

Figure 4.2: FASTA sequence of carbonic anhydrase 9, aldose reductase and estrogen receptor beta

4.3 Physicochemical Characterization of Proteins

We utilized an online tool called ProtParam to forecast a variety of parameters, including the molecular and structural properties of specific proteins [75]. Table 4.1 lists the physiochemical characteristics of carbonic anhydrase 9, aldose reductase and estrogen receptor beta.

Table 4.1: The physicochemical properties of carbonic anhydrase 9, aldose reductase and estrogen receptor beta

Target Proteins	**MW**	**PI**	**NR**	**PR**	**Ext Co1.**	**Ext Co2.**	**Instability Index**	**Aliphatic Index**	**GRAVY**
Carbonic anhydrase 9	28158.8	5.46	28	19	35075	34950	39.41	85.84	-0.274
Aldose reductase	35706.14	6.55	38	36	49765	49390	36.27	93.43	-0.27
Estrogen receptor β	30528.04	6.97	28	27	26720	26470	37.3	109	-0.121

All proteins exhibit molecular weights ranging from approximately 28 kDa to 36 kDa, with isoelectric points varying from 5.46 to 6.97, suggesting they are likely soluble under physiological conditions. The instability index values are relatively low,

indicating that these proteins are likely stable in physiological environments. Furthermore, the relative volume of aliphatic side chains is reflected by the aliphatic index is high for all proteins, suggesting a tendency for thermal stability. The GRAVY scores are negative, implying that these proteins are hydrophilic, which is beneficial for interactions with aqueous environments in biological systems. Overall, these properties suggest that the proteins are well-suited for their biological roles.

4.4 Functional Domain Identification of Proteins

In order to ascertain the domains and functional sites of specific proteins, Interpro was utilized. It is a useful tool for functional study of protein sequences. Sequence, structure, and relationships are all involved in conserved domains. Proteins can have many functional domains, each of which carries out a distinct task. The functional domain of a protein is the active region that engages in interactions between proteins and other substances.

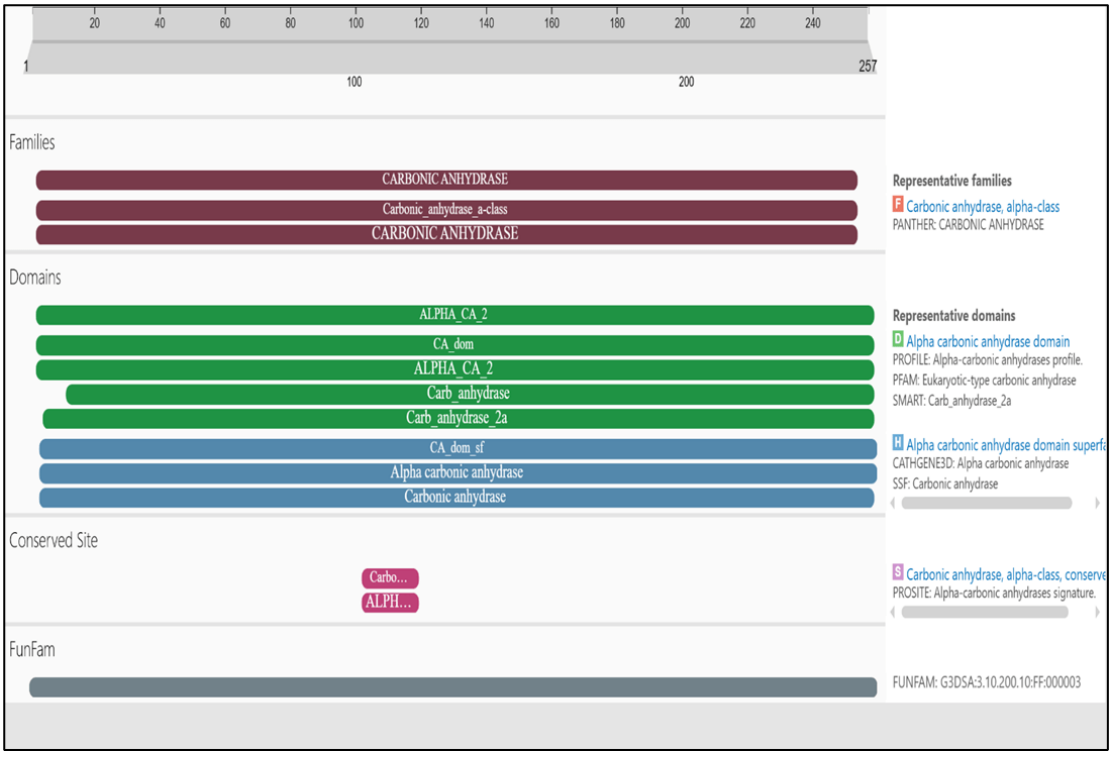


FIGURE 4.3: Domains of carbonic anhydrase 9

Figure 4.3 shows the functional domains of the protein The domains of Carbonic Anhydrase 9 are essential for its structure and functionality. Key among them is the ALPHA_CA_2 domain, characteristic of alpha-class carbonic anhydrases.

It is essential to the catalytic mechanism of the enzyme and helps convert carbon dioxide to bicarbonate. Another important domain is CA_domin, which further characterizes the enzyme's function within the carbonic anhydrase family, contributing to its overall stability and catalytic activity.

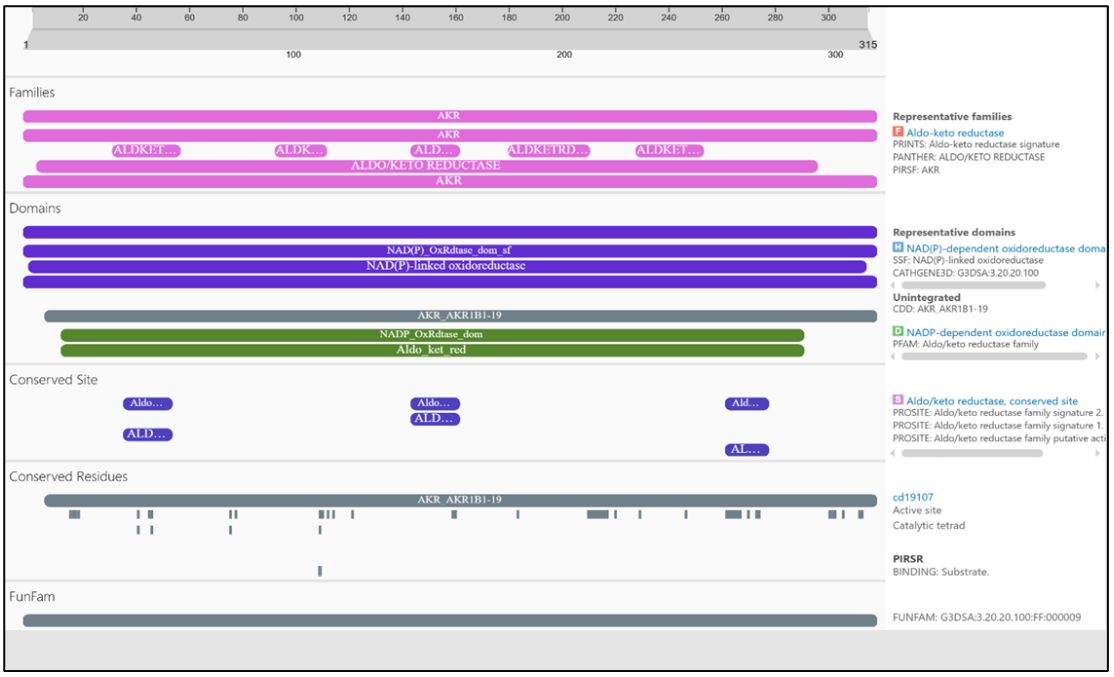


FIGURE 4.4: Domains of aldose reductase

The figure 4.4 depicts the structural domains of Aldose Reductase, highlighting key components that define its functionality. The prominent domain, NADP _oxidoreductase _dom, is crucial for the enzyme's role in catalyzing the reduction of glucose to sorbitol using NADPH as a cofactor. This domain is characteristic of enzymes that depend on NADP and is essential for the redox reactions facilitated by Aldose Reductase. Additionally, there is ALDO_reductase domain, which is fundamental to the enzyme's catalytic activity within the aldo-keto reductase family.

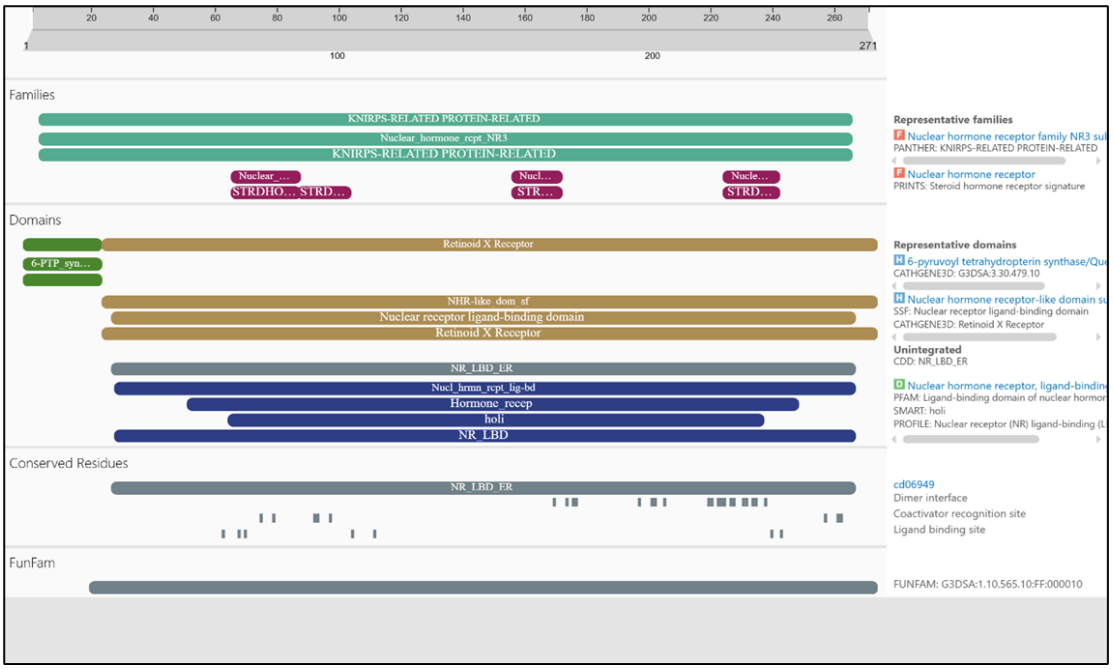


FIGURE 4.5: Domains of estrogen receptor beta

The figure 4.5 illustrates the structural domains of Estrogen Receptor Beta, highlighting crucial components that define its functionality. At the top, the Nuclear Hormone Receptor family is represented, emphasizing ERβ's role in hormone signaling. The primary domain, Nuclear Receptor Ligand Binding Domain (LBD), is essential for binding estrogen, allowing the receptor to mediate its effects on gene expression. Another key domain is the DNA Binding Domain (DBD), which facilitates the receptor's interaction with specific DNA sequences, enabling the regulation of target genes. The ER-like domain further characterizes the receptor's functionality within the nuclear hormone receptor superfamily.

4.5 Active Site Identification

The dogsitescorer software, which determines the number of pockets that can be bound and gives details on their surface area and volume, was utilized to determine the active sites of the protein. Figure 4.6 below illustrates the areas and volumes of target proteins carbonic anhydrase 9, aldose reductase and estrogen receptor beta. The coloured areas depict the active sites available for a particular protein.

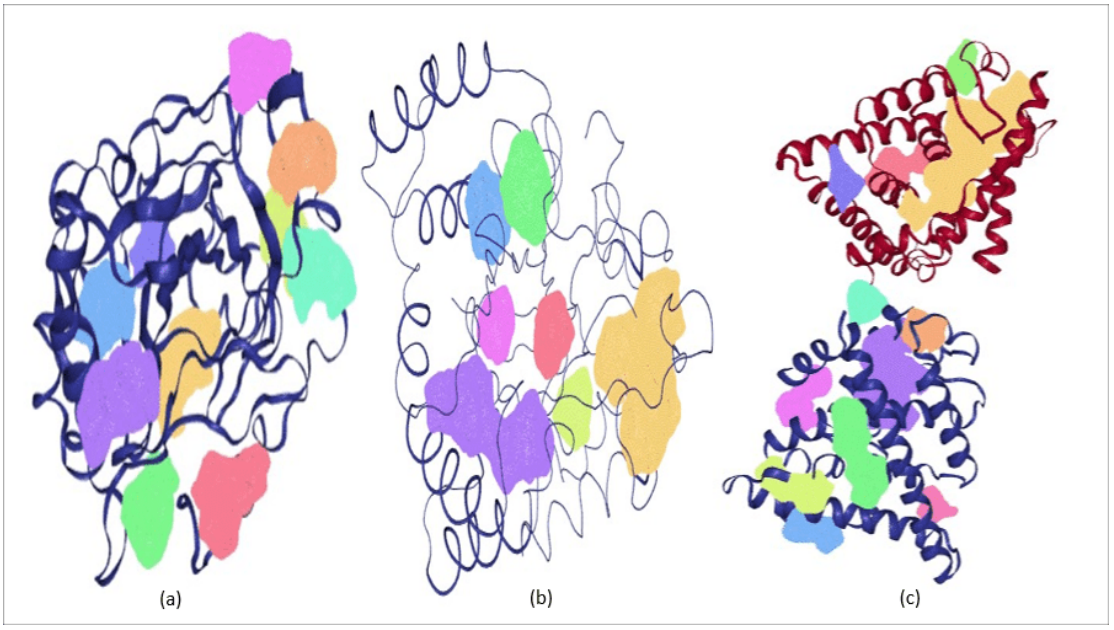


FIGURE 4.6: Active sites of (a) carbonic anhydrase 9 (b) aldose reductase (c) estrogen receptor beta

Dogsitescorer data depicts different numbers of pockets for each protein. According to this data, the carbonic anhydrase 9 consists of ten pockets while aldose reductase consists of seven pockets and estrogen receptor beta consist of 12 pockets. The number of pockets with size and volume is shown in table 4.2 below.

TABLE 4.2: Area and volume of binding pockets of carbonic anhydrase 9, aldose reductase and estrogen receptor beta

Pockets name	**Carbonic anhydrase Volume A3**	**Surface area A2**	**Pockets name**	**Aldose reductase Volume A3**	**Surface area A2**	**Pockets name**	**Estrogen receptor β Volume A3**	**Surface area A2**
P1	433.73	407.91	P1	825.02	2098.75	P1	1360.22	1539.96
P2	240.38	364.67	P2	573.18	1910.73	P2	1045.02	1123.22
P3	216.06	338.76	P3	176.13	576.95	P3	391.06	602.74
P4	210.43	432.58	P4	169.92	549.71	P4	319.3	528.55
P5	148.42	101.23	P5	139.78	528.37	P5	237.61	633.35
P6	133.06	235.02	P6	121.28	456.58	P6	223.87	538.87
P7	123.71	308.95	P7	112	427.57	P7	220.44	474.33
P8	116.8	306.84				P8	144.38	506.16
P9	107.71	242.89				P9	110.98	303.41
P10	102.21	348.48				P10	105.83	238.12
						P11	101.63	295.68
						P12	100.87	232.21

4.6 Retrieval of Chemical Structure of the Ligands

The ligand to be selected should be on the best resolution structure with that based on crystal-chemical class and their binding affinities. With that what matters is the conformational selection of the ligand. A ligand preferentially binds to one of the conformers in this selection process, boosting its numbers in comparison to the overall population and fortifying it of that protein. The largest chemical databank in the world, PubChem, was searched for ligands. These ligands' 3D structures were extracted in SDF format from the PubChem database. Table 4.3 shows all the selected ligands with the information regarding their structure.

TABLE 4.3: Chemical structure of ligands

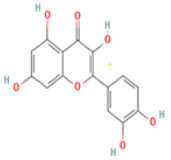
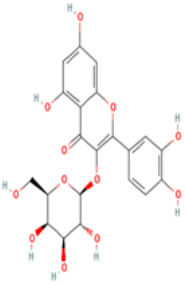
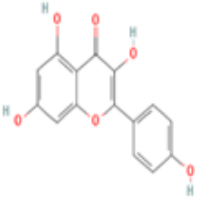
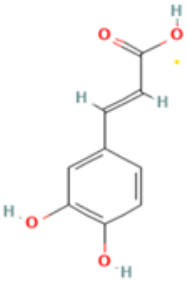
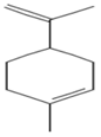
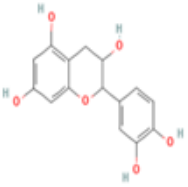
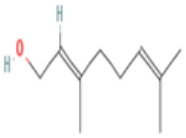
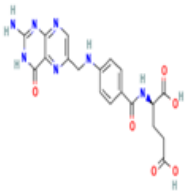
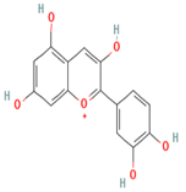
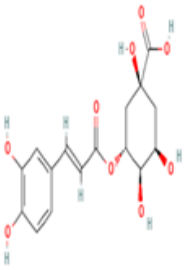
Ligand name	**Molecular weight g/mol**	**Molecular formula**	**Molecular structure**	**Smiles**
Quercetin	302.23	$C_{15}H_{10}O_7$		C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Hyperoside	464.4	$C_{21}H_{20}O_{12}$		C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O[C@H]4[C@@H]([C@H]([C@H]([C@H](O4)CO)O)O)O)O)O
Kaempferol	286.24	$C_{15}H_{10}O_6$		C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Caffeic acid	180.16	$C_9H_8O_4$		C1=CC(=C(C=C1/C=C/C(=O)O)O)O

Table 4.3 continued from previous page

Ligand name	Molecular weight g/mol	Molecular formula	Molecular structure	Smiles
Limonene	136.23	$C_{10}H_{16}$		CC1=CCC(CC1)C(=C)C
catechins	290.27	$C_{15}H_{14}O_6$		C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
Geraniol	154.25	$C_{10}H_{18}O$		CC(=CCC/C(=C/CO)/C)C
Folate	441.4	$C_{19}H_{19}N_7O_6$		C1=CC(=CC=C1C(=O)N[C@H](CCC(=O)O)C(=O)O)NCC2=CN=C3C(=N2)C(=O)NC(=N3)N
Cyanidin	287.24	$C_{15}H_{11}O_6^+$		C1=CC(=C(C=C1C2=[O+]C3=CC(=CC(=C3C=C2O)O)O)O)O
Chlorogenic acid	354.31	$C_{16}H_{18}O_9$		C1[C@H]([C@H]([C@@H](C[C@@]1(C(=O)O)O)OC(=O)/C=C/C2=CC(=C(C=C2)O)O)O)O

4.7 Energy Minimization of Ligands

After downloading the structures of the ligands that were selected the next step that was performed was minimizing the energy of these ligands. This step is an important one as we can't use simply the downloaded structure as the ligands are unstable and it can directly affect the docking vina scores. The refined structures of ligand obtained after energy minimization is given in figure 4.7.

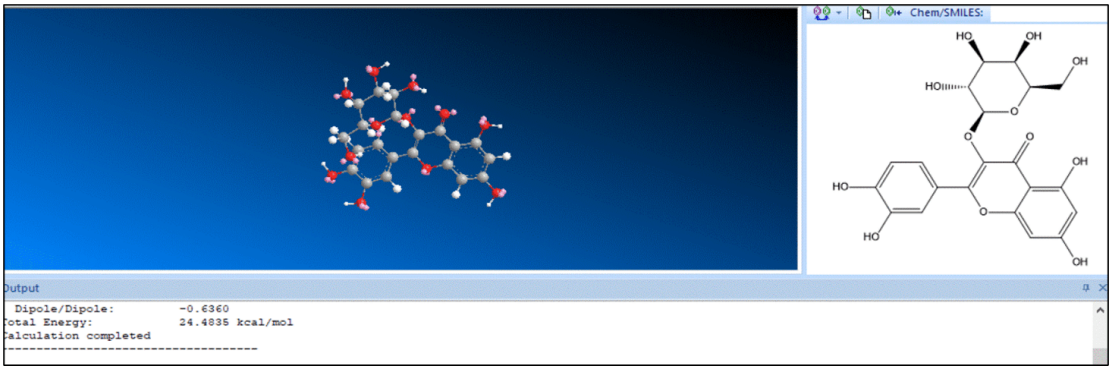


FIGURE 4.7: Energy minimization of ligands

4.8 Virtual Screening of Ligands

For compounds to be separated as both drug-like and nondrug-like virtual screening and pharmacokinetic properties are followed. The Lipinski rule deals with certain parameters like Molecular weight which should be ≤ 500, log P ≤ 5, H-bond donors ≤ 5, H-bond acceptors ≤ 10, and rotatable bonds ≤ 5. Orally active chemicals must adhere to these guidelines. The manner of administration affects the drug-like. When a chemical satisfies three or more requirements, it is classified as a drug; if it violates more than two, its absorption is poor [145]. Virtual screening of ligands is shown is table 4.4.

TABLE 4.4: Virtual screening of ligands

S.No	**Ligand name**	**Molecular weight**	**Log P value**	**Rotatable bonds**	**H-bond acceptors**	**H-bond donors**
1	Quercetin	302.238	1.988	1	7	5
2	Hyperoside	464.379	-0.5389	4	10	8
3	Kaempferol	286.239	2.2824	1	6	4
4	Caffeic acid	180.159	1.1956	2	3	3
5	Limonene	136.238	3.3089	1	0	0
6	Catechins	290.271	1.5461	1	6	5
7	Geraniol	154.253	2.6714	4	1	1
8	Folate	441.404	-0.0448	9	9	6
9	Cyanidin	287.247	2.9089	1	5	5
10	Chlorogenic acid	354.311	-0.6459	4	8	6

All ligands adhere to the Lipinski rule, as Table 4.4 demonstrates. All ligands have log P values less than 5 and the molecular weight of all is also below 500. The hydrogen bond donor, acceptor, and rotatable bonds are also in range for all ligands.

4.9 ADMET Analysis of Ligands

A second investigation was conducted utilizing the online program pkCSM to ascertain ligands' ADMET characteristics as a pharmacokinetic metric following the Lipinski rule. There are two general words in pharmacology: pharmacodynamics and pharmacokinetics.

Within the field of pharmacology, pharmacodynamics examines how medications affect the body. In pharmacokinetics, we investigate how medications are absorbed, distributed, metabolized, and excreted [146].

4.9.1 Absorption Properties of Ligands

The absorption parameters reveal important criteria for evaluating the bioavailability of compounds. For water solubility, values greater than -2 indicate better solubility, which can enhance absorption. In terms of Caco2 permeability, a good value is considered to be greater than 0, with values exceeding 1 suggesting high permeability and excellent absorption potential. Intestinal absorption is deemed favorable when values are above 50%, indicating good absorption in humans.

For skin permeability, values greater than -2 suggest better permeability, which is advantageous for topical applications. Lastly, regarding P-glycoprotein substrates, a "Yes" indicates that the compound can be actively transported by P-glycoprotein, which may be beneficial or not depending on the context.

Ideally, for P-glycoprotein inhibitors, a "No" status is preferred to avoid potential drug interactions that could compromise therapeutic efficacy [147]. The absorption properties of ligands are given in table 4.5.

TABLE 4.5: Absorption values of ligands

ADMET Properties		Quercetin	Hyperoside	Keampferol	Caffeic acid	Limonene	Catechins	Geraniol	Folate	Cyanidin	Chlorogenic acid
Absorption	Water solubility	-2.925	-2.925	-3.04	-2.33	-3.568	-3.117	-2.866	-2.88	-2.935	-2.449
	Caco2 Permeability	-0.229	0.242	0.032	0.634	1.401	-0.283	1.49	-0.88	-0.35	-0.84
	Intestinal absorption (human)	77.207	87.999	74.29	69.407	95.898	68.829	92.788	31.11	87.303	36.377
	Skin permeability	-2.735	-2.735	-2.735	-2.722	-1.721	-2.735	-1.511	-2.74	-2.735	-2.735
	P-glycoprotein substrate	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
	P-glycoprotein I inhibitor	No	No	No	No	No	No	No	No	No	No
	P-glycoprotein II inhibitor	No	No	No	No	No	No	No	No	No	No

All ligands have good water solubility. Caco2 permeability is less for some ligands, intestinal absorption is good for all ligands except folate and chlorogenic acid. Skin permeability is also in range. No ligand is inhibitor of P-glycoprotein while some ligands are identified as P-glycoprotein substrates, which could affect their systemic availability.

4.9.2 Distribution Properties of Ligands

The theoretical volume or VDss indicates the entire dosage of the medication that must be dispersed evenly to produce a concentration similar to that of blood plasma. For VDss a good value is typically greater than 0.5 L/kg, indicating favorable distribution in body tissues. The fraction unbound (Fu) should ideally be above 0.1, which signifies a significant proportion of the drug is available for

therapeutic action. The blood-brain barrier reduces the amount of exogenous substances that can reach the brain directly while protecting it. Regarding BBB permeability (log BB), values greater than 0 suggest the ability to cross the blood-brain barrier. For CNS permeability (log PS), values closer to 0, ideally above -2 are preferred, as they indicate potential for penetration into the central nervous system Table 4.6 shows the distribution properties of ligands [148]. The table indicates all ligands have safe range which is given below.

TABLE 4.6: Distribution values of ligands

ADMET Properties		**Quercetin**	**Hyperoside**	**Keampferol**	**Caffeic acid**	**Limonene**	**Catechins**	**Geraniol**	**Folate**	**Cyanidin**	**Chlorogenic acid**
Distribution	VDss (human)	1.559	1.846	1.274	1.098	0.396	1.027	0.17	0.046	0.952	0.581
	Fraction unbound (human) Fu	0.206	0.228	0.178	0.529	0.48	0.235	0.447	0.37	0.243	0.658
	BBB permeability log BB	-1.098	-1.688	-0.939	-0.647	-0.732	-1.054	-0.606	-1.62	-1.234	-1.407
	CNS permeability log PS	-3.065	-4.093	-2.228	-2.608	-2.37	-3.298	-2.159	-4.26	-2.218	-3.856

VDSS and fraction unbound values are in range for all ligands. The BBB and CNS value are negative indicating they cannot cross the blood brain barriers and the CNS.

4.9.3 Metabolism Properties of Ligands

The enzyme cytochrome P450 is in charge of the liver's detoxification process. Many drugs get deactivated by this enzyme but certain drugs are capable of activating. This enzyme's inhibitors can directly affect the metabolism of the drug hence should not be used. Similarly, CYP2D6 and CYP3A4 are responsible for the drugs' metabolism. Inhibition of these affects the pharmacokinetics of the drug

in use [149]. The ligand metabolism prediction is shown below. The metabolic characteristics of ligands are displayed in Table 4.7.

TABLE 4.7: Metabolism values of ligands

ADMET Properties			Quercetin	Hyperoside	Keampferol	Caffeic acid	Limonene	Catechins	Geraniol	Folate	Cyanidin	Chlorogenic acid
Metabolism	CYP2D6 substrate	sub-	No	No	No	No	No	No	No	No	No	No
	CYP3A4 substrate	sub-	No	No	No	No	No	No	No	No	No	No
	CYP1A2 hibitor	in-	Yes	No	Yes	No	No	No	No	No	Yes	No
	CYP2C19 hibitor	in-	No	No	No	No	No	No	No	No	No	No
	CYP2C9 hibitor	in-	No	No	No	No	No	No	No	No	No	No
	CYP2D6 hibitor	in-	No	No	No	No	No	No	No	No	No	No
	CYP3A4 hibitor	in-	No	No	No	No	No	No	No	No	No	No

The metabolic properties of the ligands indicate that none of the compounds are substrates for the CYP2D6 or CYP3A4 enzymes, which suggests they are not metabolized by these pathways. This is beneficial as it reduces potential drug interactions that could arise from competition for these important metabolic enzymes. Quercetin, keampferol and cyanidin show inhibition of the CYP1A2 enzyme, which can lead to increased levels of drugs metabolized by this enzyme.

4.9.4 Excretion Properties of Ligands

Two organs are involved in drug excretion, the liver, which is engaged in biliary excretion, and the kidneys, which are involved in renal excretion. Excretion may

also include other organs, such as the lungs in the case of volatile or gaseous substances. Moreover, drugs can be expelled through tears, saliva, and perspiration [150]. The excretion values of the ligands are given in table 4.8.

TABLE 4.8: Excretion values of ligands

ADMET Properties			Quercetin	Hyperoside	Keampferol	Caffeic acid	Limonene	Catechins	Geraniol	Folate	Cyanidin	Chlorogenic acid
Excretion	Total Clearance		0.407	0.494	0.477	0.508	0.213	0.183	0.437	0.527	0.532	0.307
	Renal substrate	OCT2	No	No	No	No	No	No	No	No	No	No

The total clearance values for the compounds are in range. Notably, all compounds are classified as non-substrates for renal OCT2, which implies that they do not rely on this renal transport mechanism for excretion. This is beneficial as it minimizes the risk of interactions with other drugs that may utilize the same pathway.

4.9.5 Toxicity Properties of Ligands

By using pkCSM we determined the toxicity of the ligands. AMES toxicity test is used to test the mutagenic potential of the compound by using bacteria. If it shows a positive response, then the ligand is mutagenic which can also act as a carcinogen. The toxicity of *T. Pyriformis* (protozoa bacterium) is used as a toxic endpoint in the *T. Pyriformis* toxicity method. Any value ¿-0.5 log ug/L is considered toxic. The values predicted in the Minnow toxicity test are used to represent the concentration at which the compound could cause the death of 50% of the minnows. The value below 0.5 mM is regarded as acute toxic [151]. The anticipated log value of the lowest observed adverse effect in the oral rat chronic toxicity test impact is correlated with the drug concentration that requires a specific duration of treatment, expressed in log mg/kg bw/day. A hepatotoxicity test predicts that if a compound could affect liver functioning or not. Higher

maximum tolerated dose (MRTD) values indicate better safety [152]. The toxicity values of all ligands are given in table 4.9.

TABLE 4.9: Toxicity values of ligands

	ADMET Properties	Quercetin	Hyperoside	Keampferol	Caffeic acid	Limonene	Catechins	Geraniol	Folate	Cyanidin	Chlorogenic acid
Toxicity	AMES toxicity	No	No	No	No	No	No	No	No	No	No
	Max tolerated dose (human)	0.499	0.569	0.531	1.145	0.777	0.438	0.65	0.586	0.497	0.134
	hERG I inhibitor	No	No	No	No	No	No	No	No	No	No
	hERG II inhibitor	No	No	No	No	No	No	No	No	No	No
	Oral rat acute toxicity (LD50)	2.471	2.541	0.449	2.383	1.88	2.428	1.636	2.67	2.464	1.973
	Oral rat chronic toxicity (LOAEL)	2.612	4.417	2.505	2.092	2.336	2.5	2.03	3.153	2.542	2.982
	Hepatotoxicity	No	No	No	No	No	No	No	No	No	No
	Skin sensitization	No	No	No	No	No	No	No	No	No	No

No inhibition of hERG I or hERG II was seen in any ligand. None of the ligands demonstrated hepatotoxicity, AMES toxicity and skin sensitivity. Every ligand's MRTD value is within the range. *T. pyriformis* activity was seen in all ligands at least 0.5 log µg/L. The tolerable threshold of 0.5 mM was exceeded by the minnow toxicity levels of all ligands.

4.10 Molecular Docking

To carry out docking, the three-dimensional structures of the protein and ligands are used. An online blind auto docking program called CB dock is utilized for this. CB Dock computes the cavity sizes and predicts the protein binding locations. CB Dock provides us with the top five possess and receptor models upon docking. Based on the cavity size and the vina score, the optimal position was chosen among

these five [153]. Molecular docking was performed by using carbonic anhydrase 9, aldose reductase and estrogen receptor beta as the receptor proteins and quercetin, hyperoside, kaempferol, caffeic acid, limonene, catechins, geraniol, folate, cyanidin and chlorogenic acid as ligands. The ligands are in SDF format, while the proteins are in PDB format. After verifying the input files, CB Dock uses Open Babel and MGL tools to transform them into files in the pdbqt format. Next, CB dock determines the receptor's cavities as well as the diameters and centers of the top five cavities. The protein-ligand interaction's high-affinity score determines which of the five optimal conformations is the best [154]. The scores obtained after the docking of proteins and ligands are shown in tables 4.10.

TABLE 4.10: Docking score of ligand-protein complexes

Target Proteins	**Ligands**									
	Quercetin	**Hyperoside**	**Kaempferol**	**Caffeic acid**	**Limonene**	**Catechins**	**Geraniol**	**Folate**	**Cyanidin**	**Chlorogenic acid**
Carbonic anhydrase 9	-7.5	-8.2	-7.2	-6.4	-4.9	-7.2	-5.4	-8.1	-7.4	-7.6
Aldose reductase	-9.6	-10.5	-9.4	-7.3	-6.5	-9.2	-6.1	-10.2	-9.9	-9.4
Estrogen receptor β	-8.9	-8.9	-8.7	-6.2	-5.9	-8.8	-6.1	-7.7	-8.5	-8.2

Table 4.10 shows the docking result of receptors with ligands. It shows that carbonic anhydrase has the highest binding score of -8.2 with hyperoside. Aldose reductase has a binding score of -10.5 with hyperoside whereas estrogen receptor beta has a binding score of -8.9 with quercetin.

4.11 Analysis of Docked Complexes via Discovery Studio

To understand docking data, ligand and protein interaction was estimated. Hydrogen bonding, alkyl and van der waals interactions are the main types of interactions that were investigated. Discovery Studio 2025 Client was used to analyze

these interactions between proteins and ligands. The saved conformations for the ligand-receptor complex of each molecule were analyzed in detail. This program creates schematic representations of the protein-ligand interactions between the specified ligands in the PDB file automatically. The docked files were uploaded in PDB format and a significant number of interactions were observed between the ten ligands and the three target proteins [155]. The following diagrams show the docked complexes along with ligand-receptor interactions.

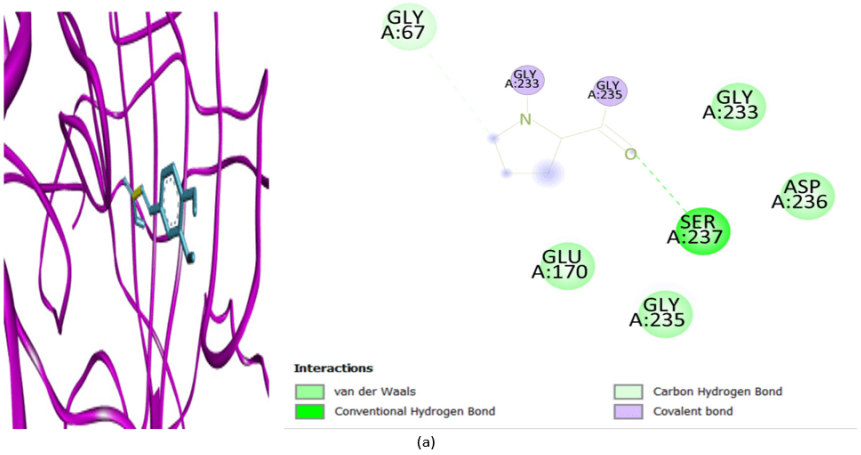


FIGURE 4.8: Analysis of dock complexes of carbonic anhydrase with caffeic acid

Figure 4.8 shows the interaction of carbonic anhydrase with caffeic acid. It shows that there is one hydrogen bond with Serine 237, four van der waals interactions and two covalent connections.

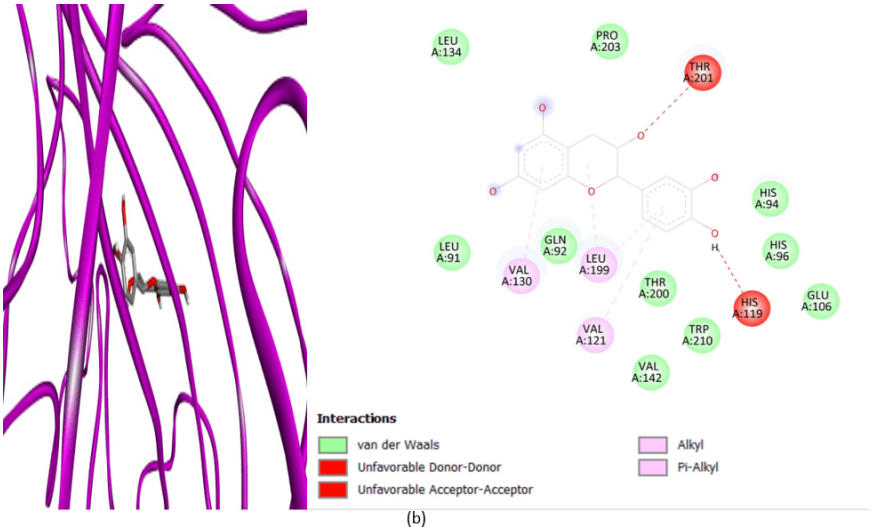


FIGURE 4.9: Analysis of dock complexes of carbonic anhydrase with catechins

Figure 4.9 shows the interaction of carbonic anhydrase with catechins. It shows that there are three alkyl bonds and two unfavorable interactions. Moreover, there are ten van der waals interactions.

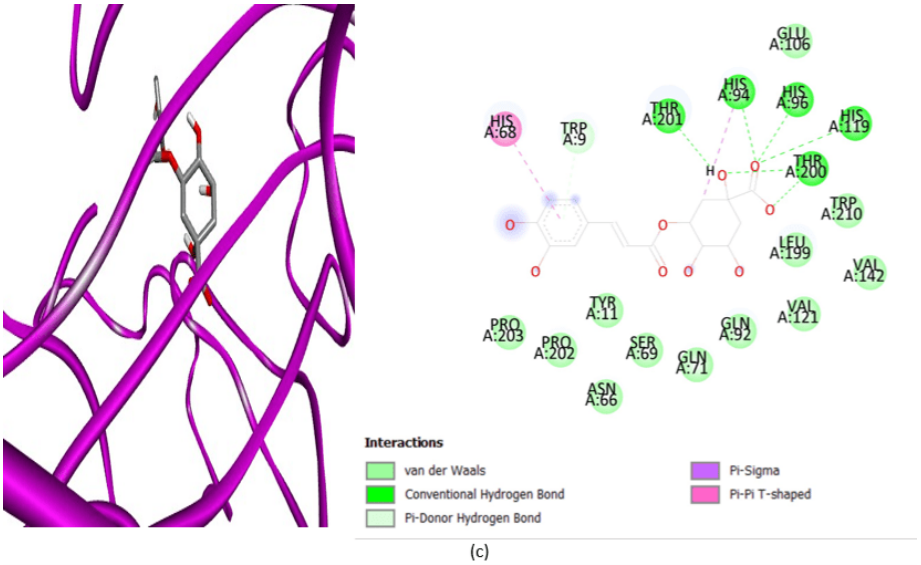


FIGURE 4.10: Analysis of dock complexes of carbonic anhydrase with chlorogenic acid

Figure 4.10 shows the interaction of carbonic anhydrase with chlorogenic acid. It demonstrates that there are twelve van der waals interactions and five hydrogen bonds.

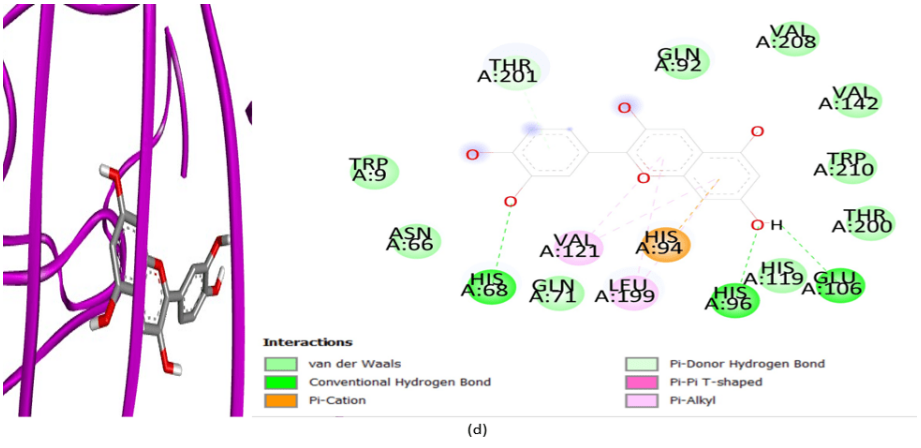


FIGURE 4.11: Analysis of dock complexes of carbonic anhydrase with cyanidin

Figure 4.11 shows the interaction of carbonic anhydrase with cyanidin. It shows that there are nine van der waals contacts and three hydrogen bonds together.

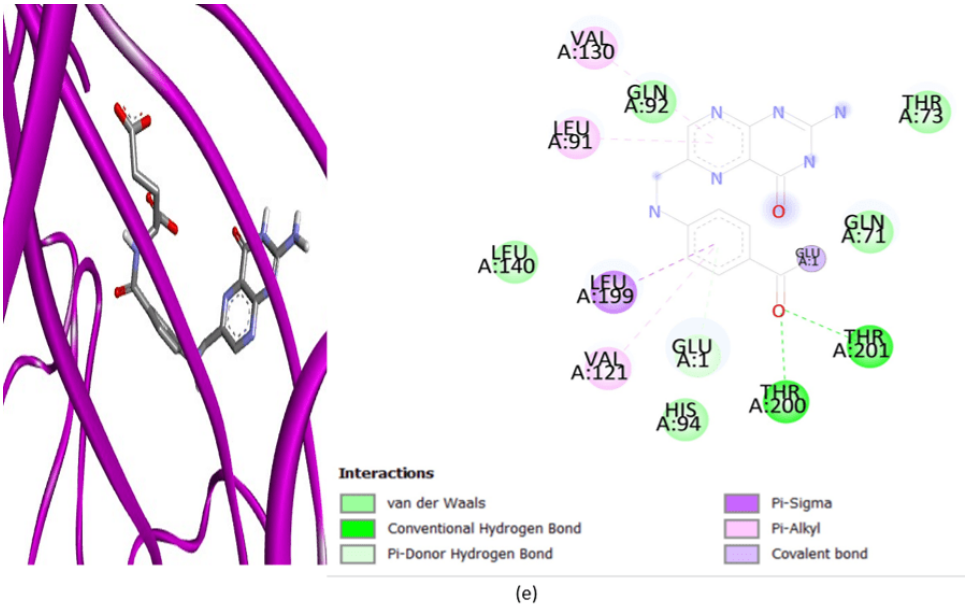


FIGURE 4.12: Analysis of dock complexes of carbonic anhydrase with folate

Figure 4.12 shows the interaction of carbonic anhydrase with folate. It shows that there are two hydrogen bonds, one covalent bond and five van der waals interactions.

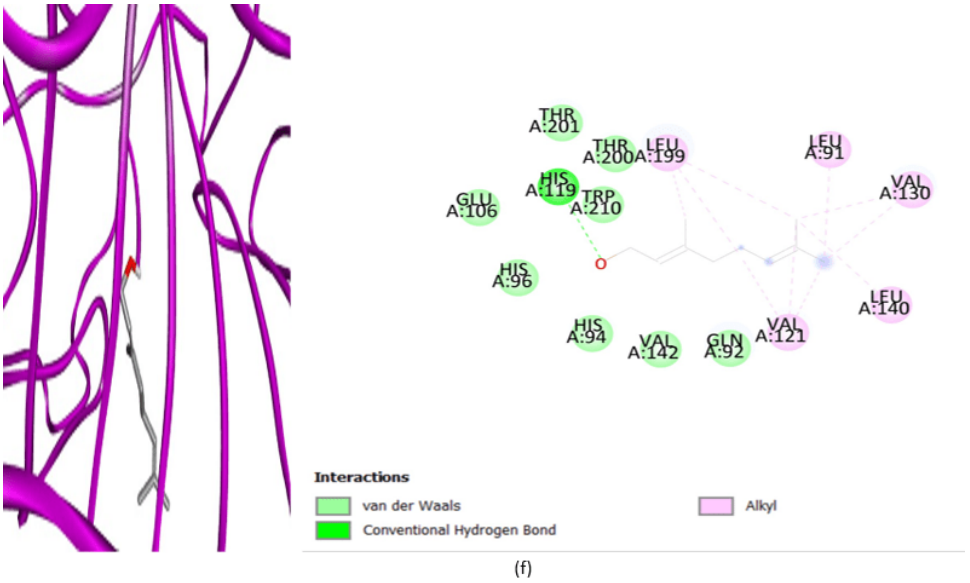


FIGURE 4.13: Analysis of dock complexes of carbonic anhydrase with geraniol

Figure 4.13 shows the interaction of carbonic anhydrase with geraniol. It shows that there is one hydrogen bond, eight van der waals and five alkyl interactions.

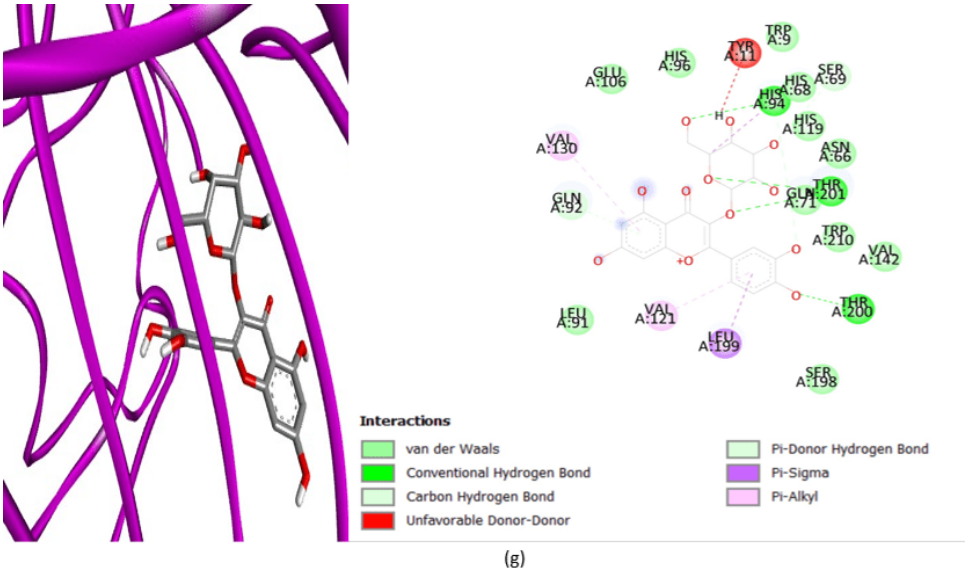


FIGURE 4.14: Analysis of dock complexes of carbonic anhydrase with hyperoside

Figure 4.14 shows the interaction of carbonic anhydrase with hyperoside. It shows that there are twelve van der waals contacts and three hydrogen bonds together.

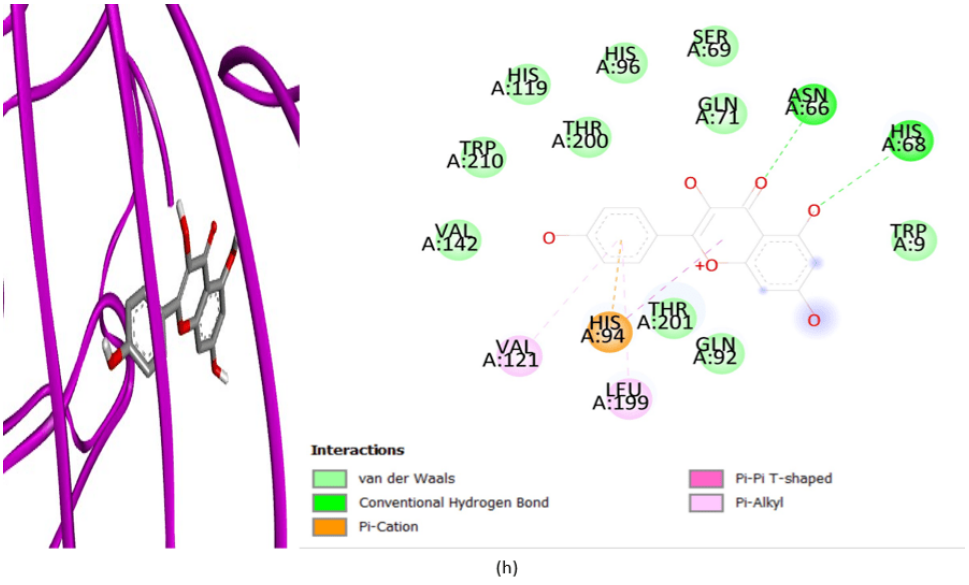


FIGURE 4.15: Analysis of dock complexes of carbonic anhydrase with kaempferol

Figure 4.15 shows the interaction of carbonic anhydrase with kaempferol. It shows that there are ten van der waals contacts and two hydrogen bonds together.

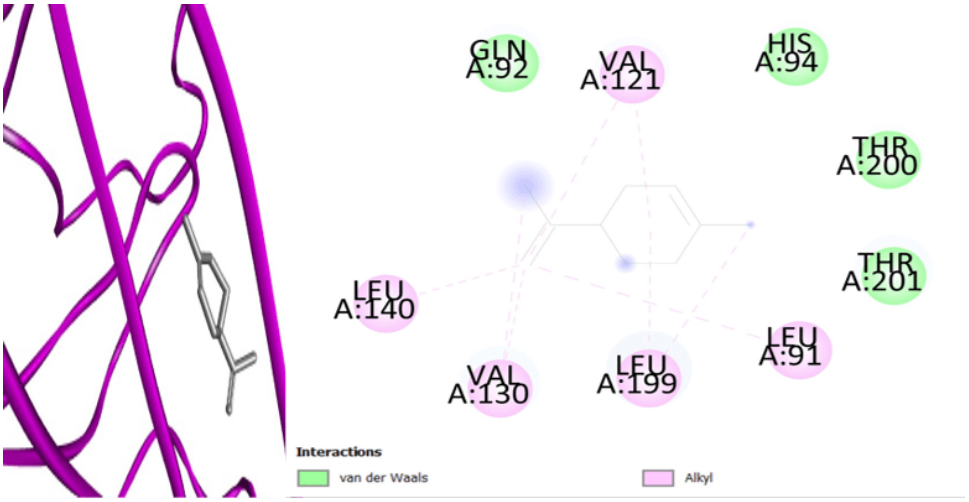


FIGURE 4.16: Analysis of dock complexes of carbonic anhydrase with limonene

Figure 4.16 shows the interaction of carbonic anhydrase with limonene. It shows that there are four van der waals interactions and five alkyl bonds are present.

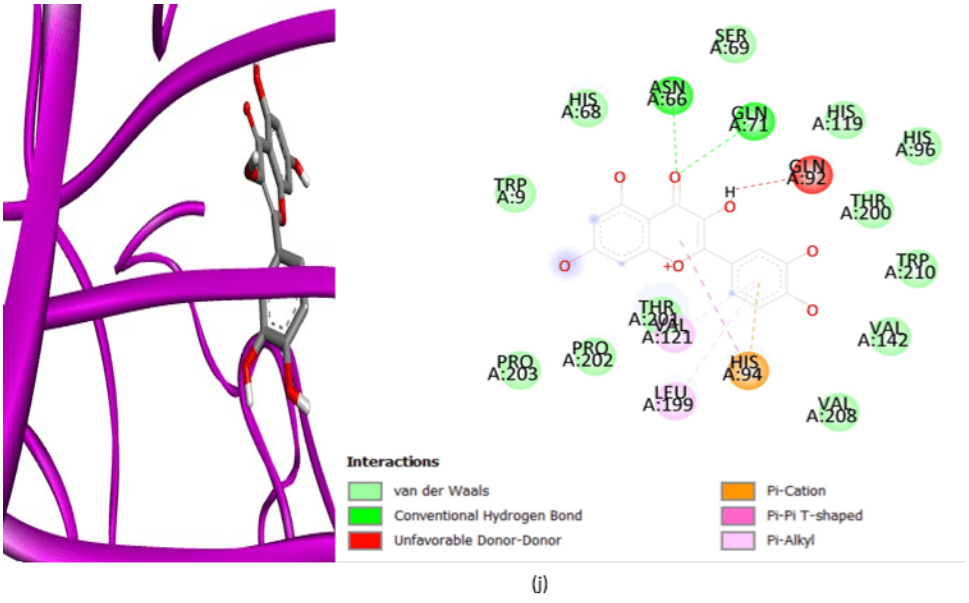
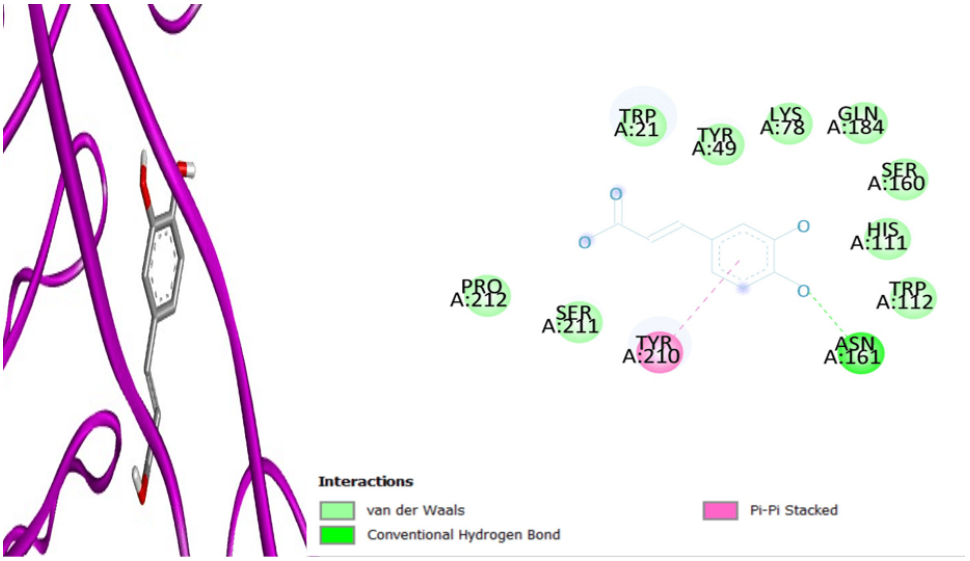


FIGURE 4.17: Analysis of dock complexes of carbonic anhydrase with quercetin

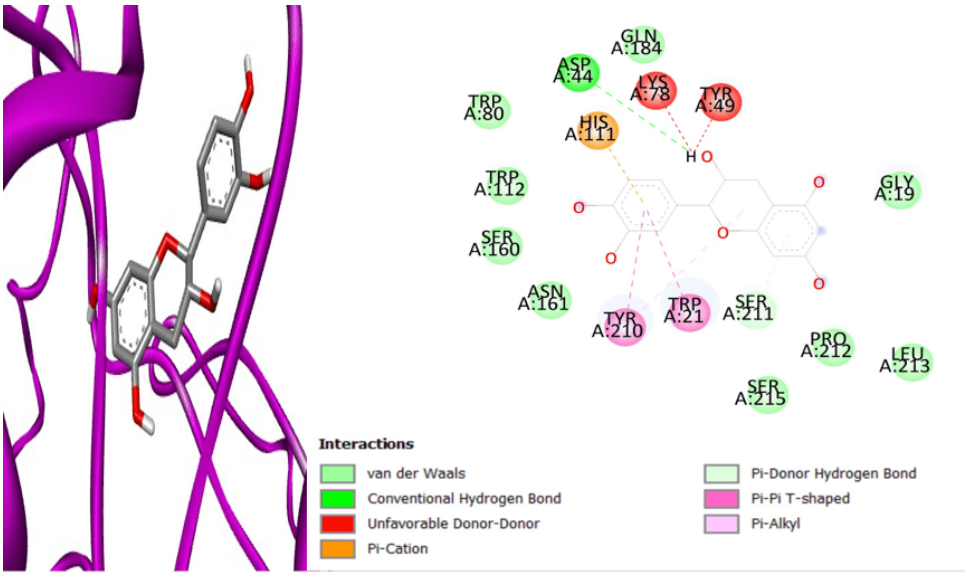
Figure 4.17 shows the interaction of carbonic anhydrase with quercetin. It shows that there are twelve van der waals contacts and two hydrogen bonds.



(a)

FIGURE 4.18: Analysis of dock complexes of aldose reductase with caffeic acid

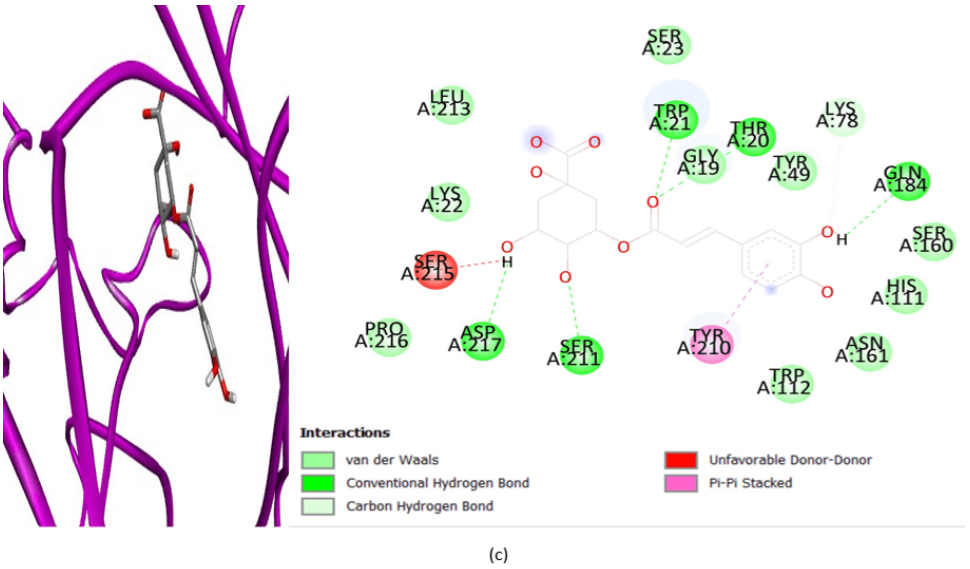
Figure 4.18 shows the interaction of aldose reductase with caffeic acid. It shows that there is one hydrogen bond and nine van der waals interactions.



(b)

FIGURE 4.19: Analysis of dock complexes of aldose reductase with catechins

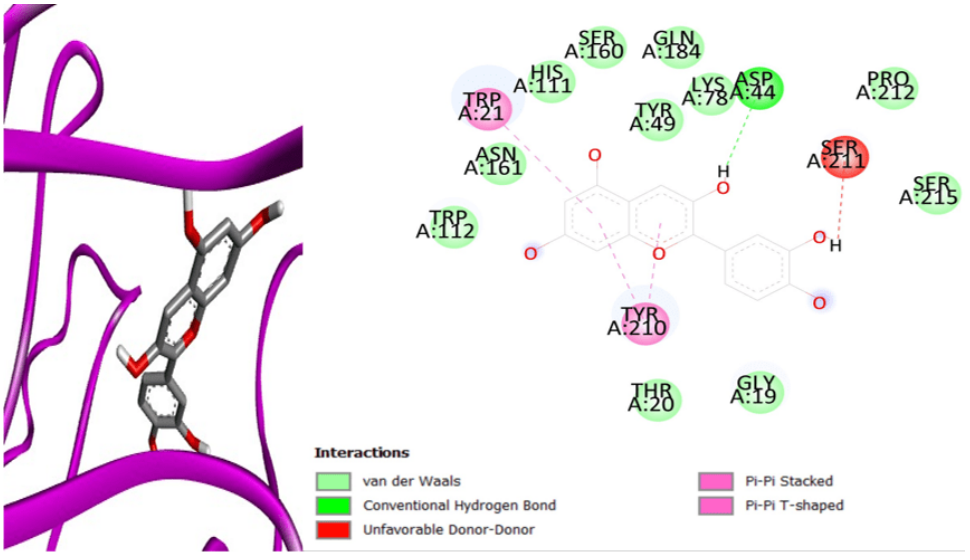
Figure 4.19 shows the interaction of aldose reductase with catechins. It shows that there is one hydrogen bond and ten van der waals interactions.



(c)

FIGURE 4.20: Analysis of dock complexes of aldose reductase with chlorogenic acid

Figure 4.20 shows the interaction of aldose reductase with chlorogenic acid. It shows that there are ten van der waals interactions and five hydrogen bonds.



(d)

FIGURE 4.21: Analysis of dock complexes of aldose reductase with cyanidin

Figure 4.21 shows the interaction of aldose reductase with cyanidin. It shows that there is one hydrogen bond and eleven van der waals interactions.

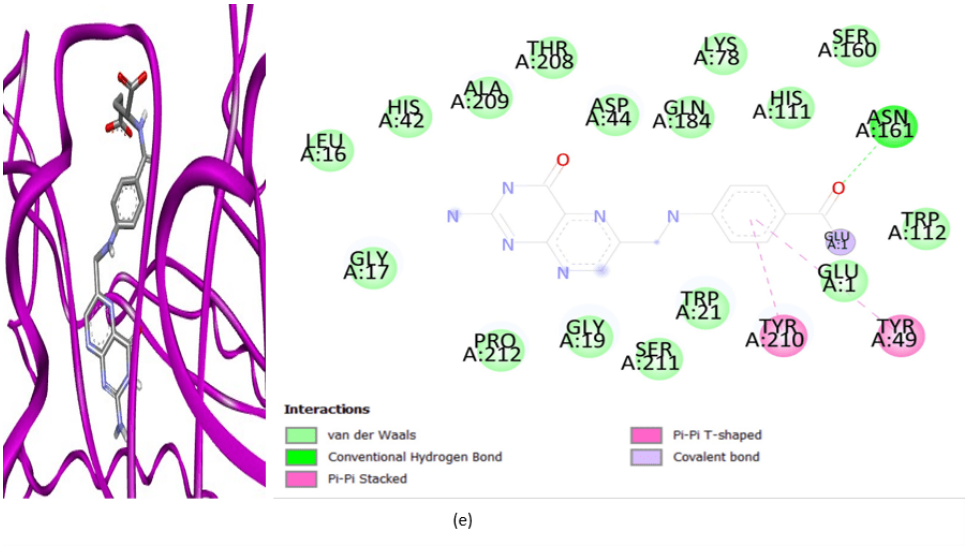


FIGURE 4.22: Analysis of dock complexes of aldose reductase with folate

Figure 4.22 shows the interaction of aldose reductase with folate. It shows that there is one hydrogen bond, one covalent bond and sixteen van der waals interactions.

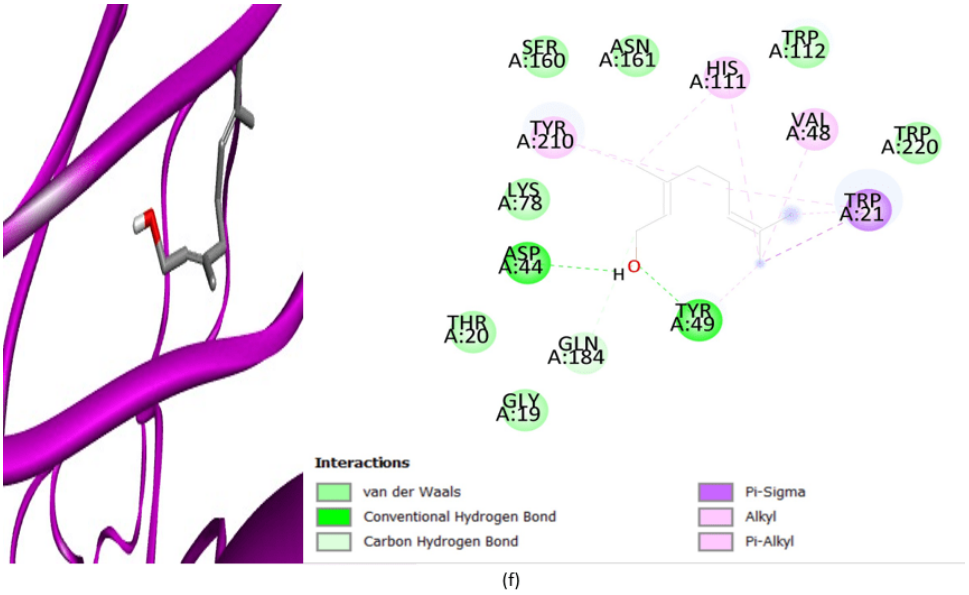
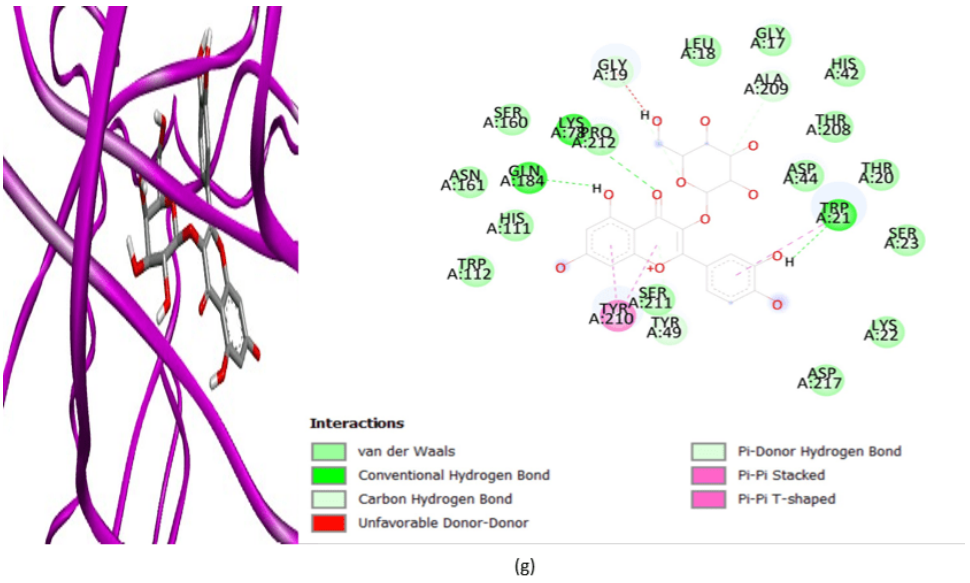


FIGURE 4.23: Analysis of dock complexes of aldose reductase with geraniol

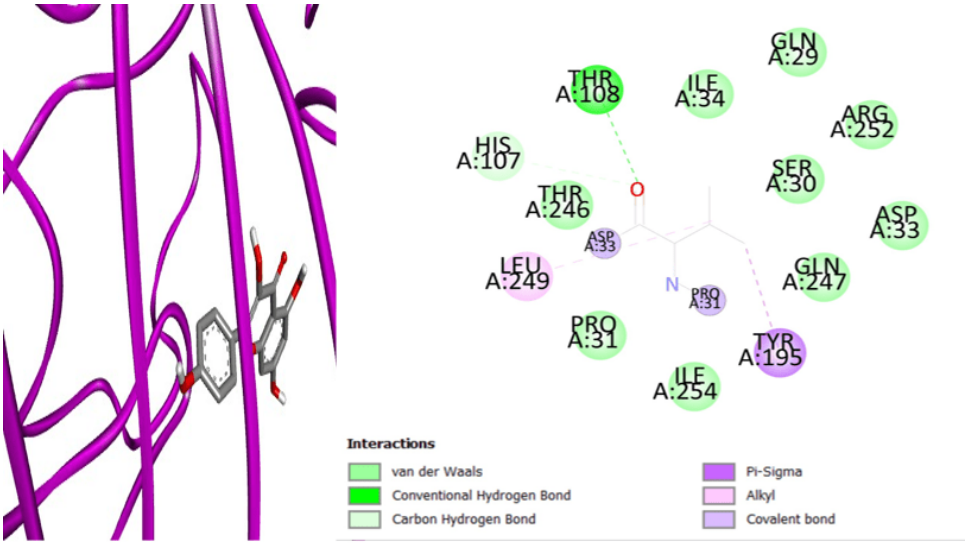
Figure 4.23 shows the interaction of aldose reductase with geraniol. It shows that there are two hydrogen bonds, three alkyl and seven van der waals interactions.



(g)

FIGURE 4.24: Analysis of dock complexes of aldose reductase with hyperoside

Figure 4.24 shows the interaction of aldose reductase with hyperoside. It shows that there are sixteen van der waals contacts and three hydrogen bonds.



(h)

FIGURE 4.25: Analysis of dock complexes of aldose reductase with kaempferol

Figure 4.25 shows the interaction of aldose reductase with kaempferol. It shows that there is one hydrogen bond, nine van der waals contacts and two covalent connections.

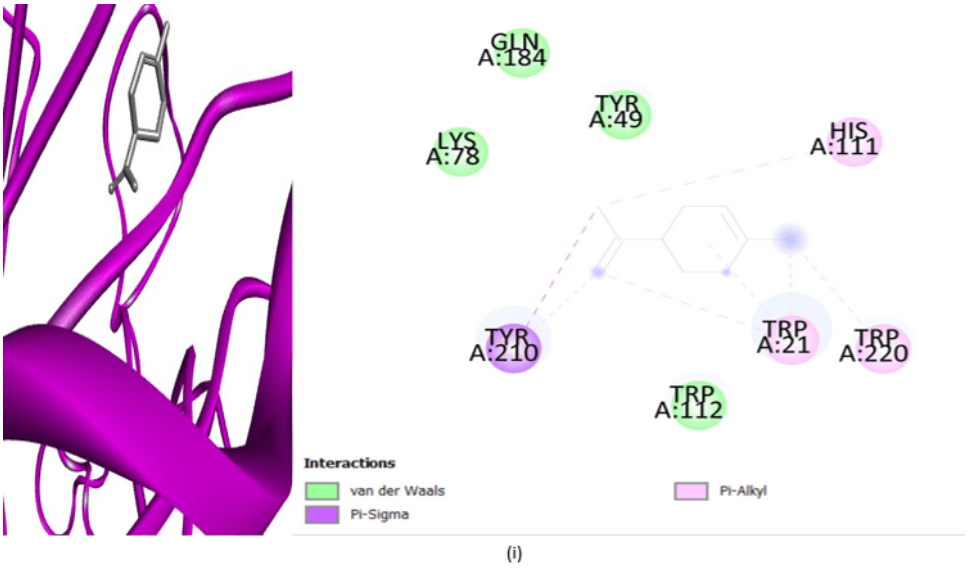


FIGURE 4.26: Analysis of dock complexes of aldose reductase with limonene

Figure 4.26 shows the interaction of aldose reductase with limonene. It shows that there are three alkyl and one sigma bond. Moreover, there are four van der waals interactions.

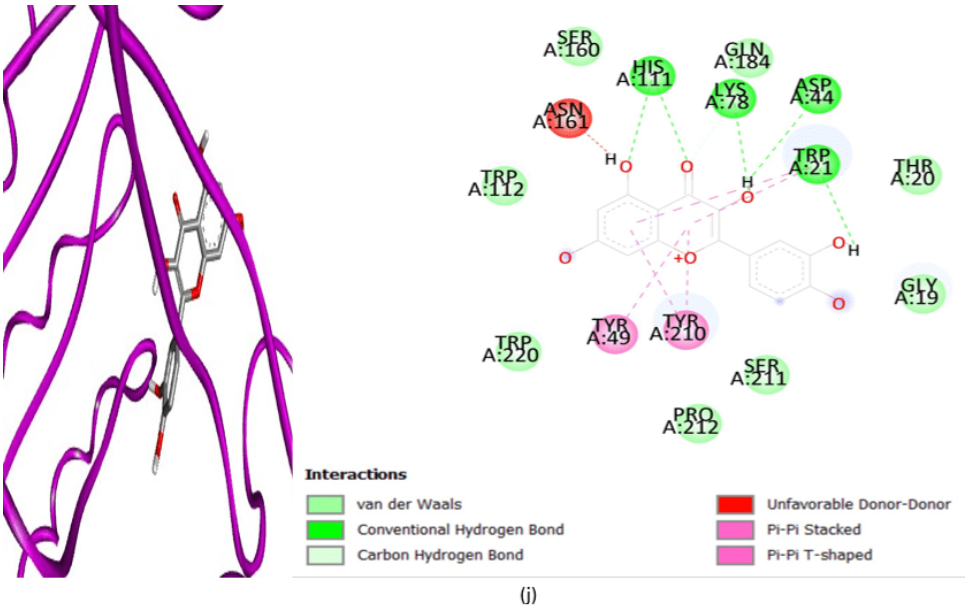


FIGURE 4.27: Analysis of dock complexes of aldose reductase with quercetin

Figure 4.27 shows the interaction of aldose reductase with quercetin. It shows that there are eight van der waals contacts and four hydrogen bonds together.

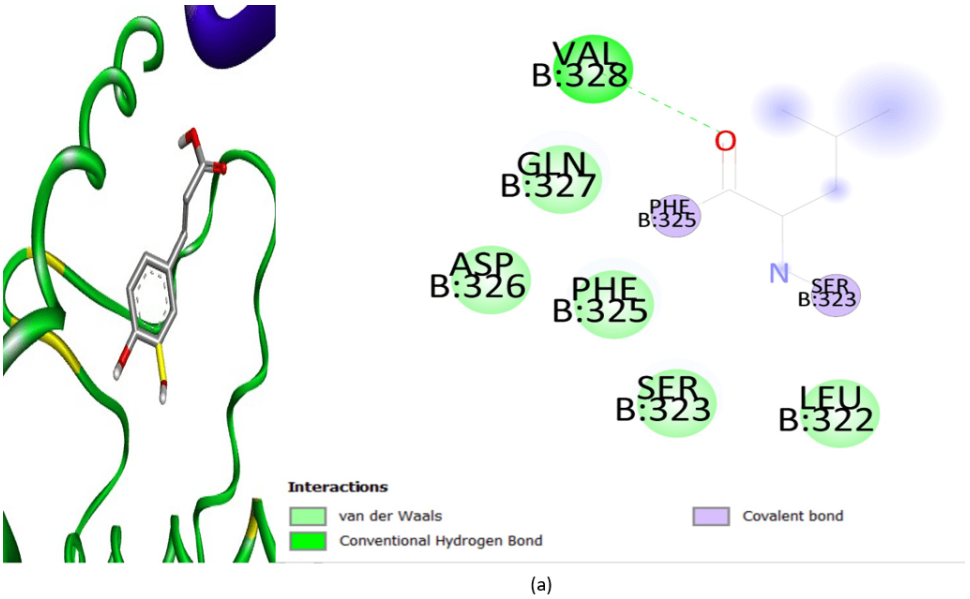


FIGURE 4.28: Analysis of dock complexes of Estrogen Receptor Beta with caffeic acid

Figure 4.28 shows the interaction of Estrogen Receptor Beta with caffeic acid. It shows that there is one hydrogen bond, five van der waals interactions and two covalent connections.

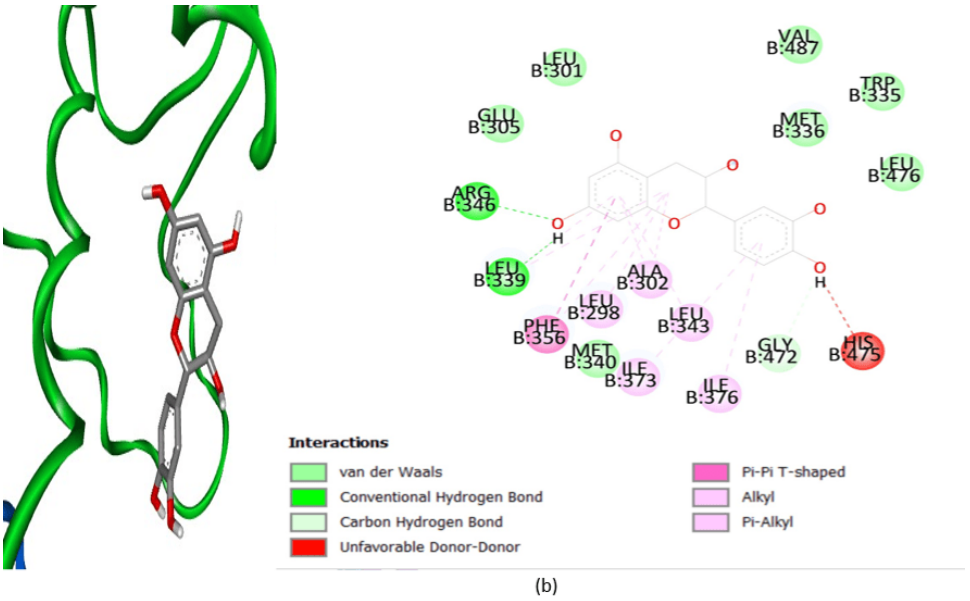


FIGURE 4.29: Analysis of dock complexes of Estrogen Receptor Beta with catechins

Figure 4.29 shows the interaction of Estrogen Receptor Beta with catechins. It shows that there are two hydrogen and five alkyl and seven van der waals contacts.

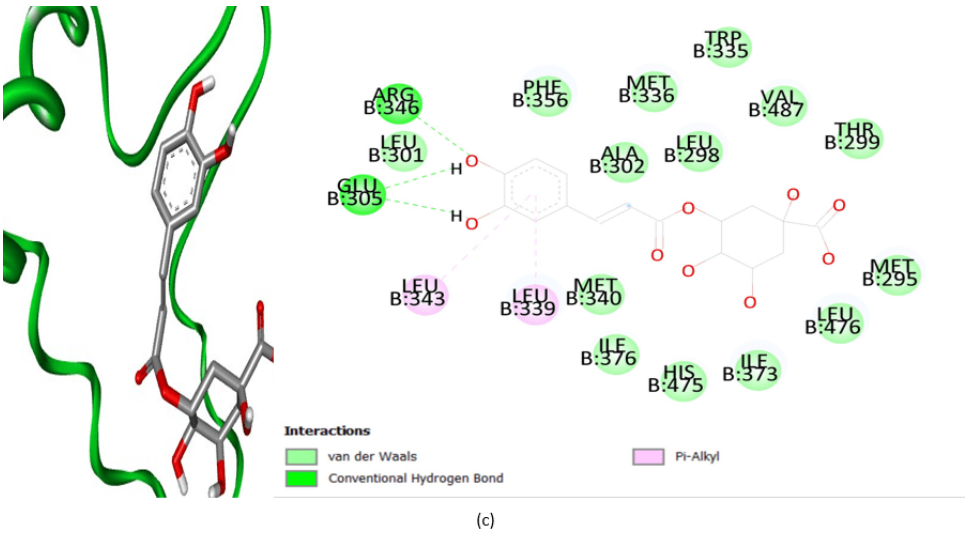


FIGURE 4.30: Analysis of dock complexes of Estrogen Receptor Beta with chlorogenic acid

Figure 4.30 shows the interaction of Estrogen Receptor Beta with chlorogenic acid. It shows that there are two hydrogen bonds and fourteen van der waals connections.

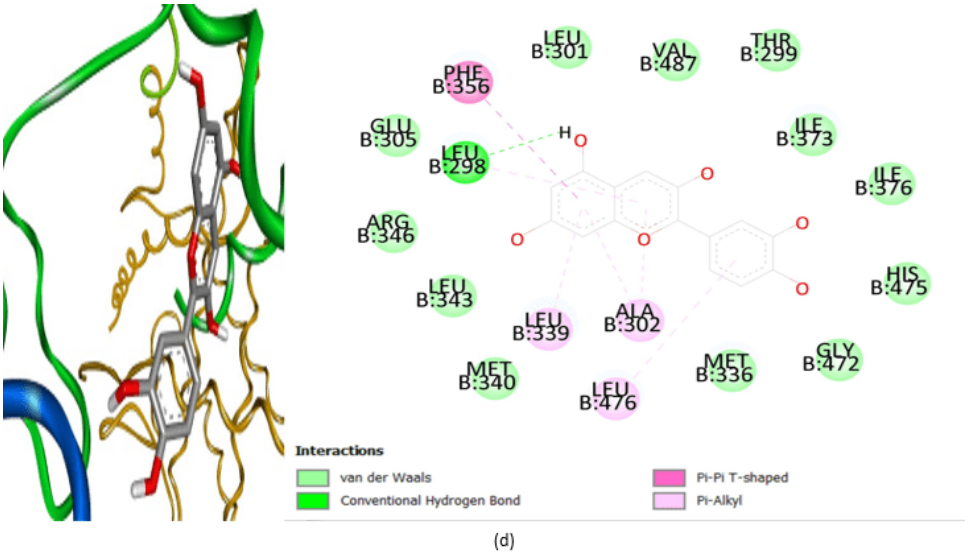


FIGURE 4.31: Analysis of dock complexes of Estrogen Receptor Beta with cyanidin

Figure 4.31 shows the interaction of Estrogen Receptor Beta with cyanidin. It shows that there is one hydrogen bond and twelve van der waals interactions.

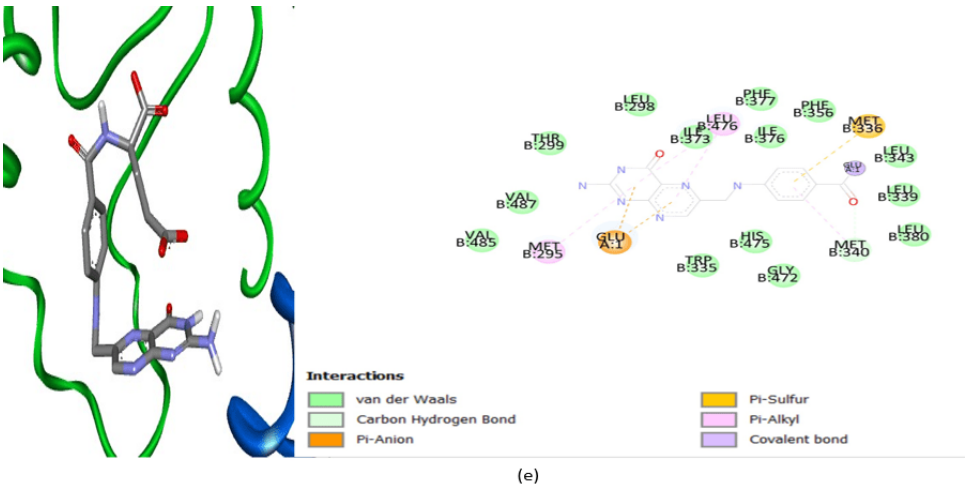


FIGURE 4.32: Analysis of dock complexes of Estrogen Receptor Beta with folate

Figure 4.32 shows the interaction of Estrogen Receptor Beta with folate. It shows that there is one carbon hydrogen bond and fourteen van der waals interactions.

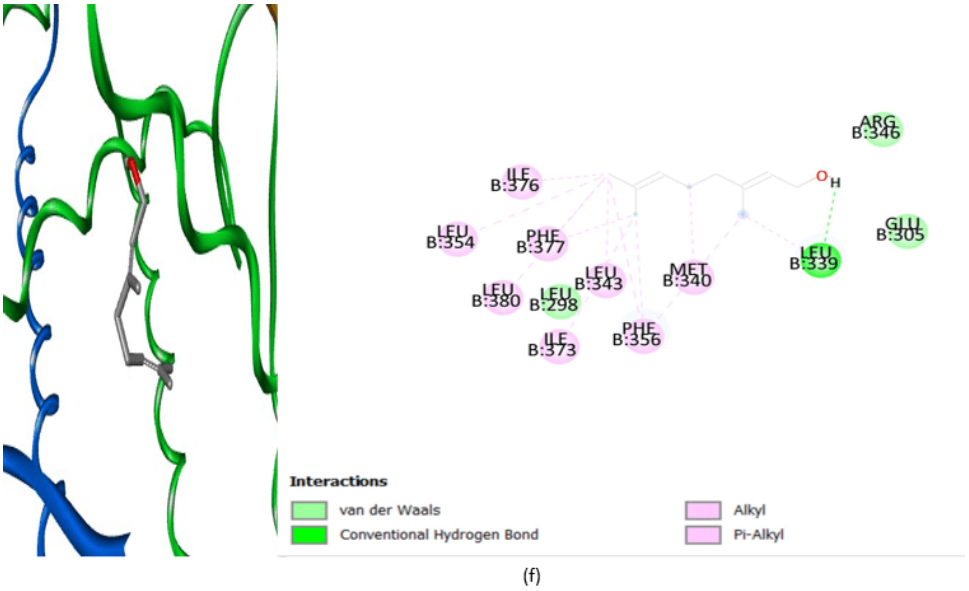


FIGURE 4.33: Analysis of dock complexes of Estrogen Receptor Beta with geraniol

Figure 4.33 shows the interaction of Estrogen Receptor Beta with geraniol. It shows that there is one hydrogen and eight alkyl and three van der waals connections.

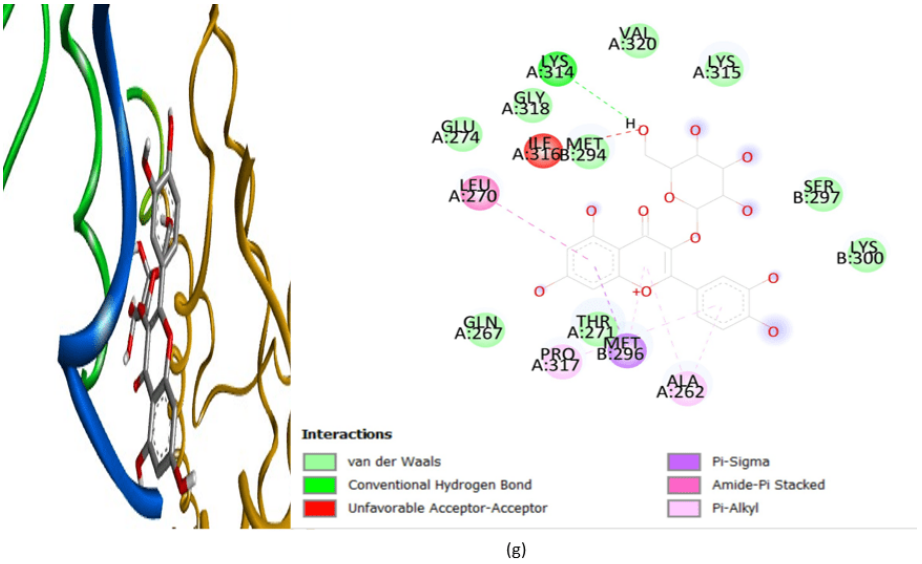


FIGURE 4.34: Analysis of dock complexes of Estrogen Receptor Beta with hyperoside

Figure 4.34 shows the interaction of Estrogen Receptor Beta with hyperoside. It shows that there is one hydrogen bond, two alkyl and nine van der waals interactions.

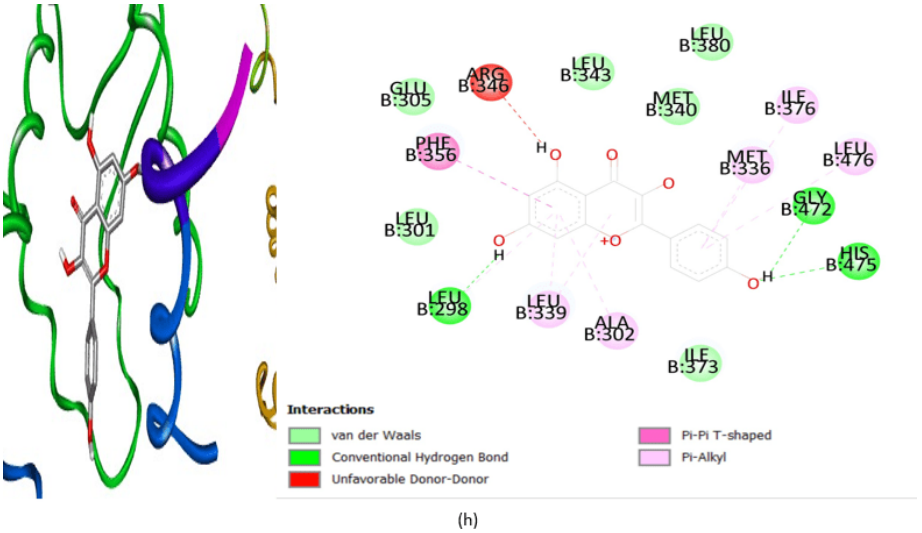


FIGURE 4.35: Analysis of dock complexes of Estrogen Receptor Beta with kaempferol

Figure 4.35 shows the interaction of Estrogen Receptor Beta with kaempferol. It shows that there are three hydrogen bonds, five alkyl and six van der waals interactions.

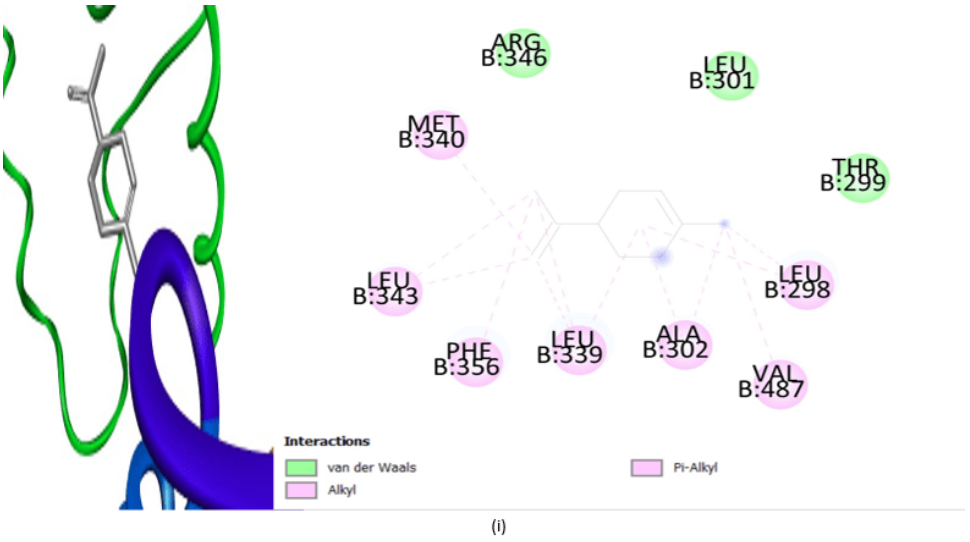


FIGURE 4.36: Analysis of dock complexes of Estrogen Receptor Beta with limonene

Figure 4.36 shows the interaction of Estrogen Receptor Beta with limonene. It shows that there are seven alkyl and three van der waals interactions.

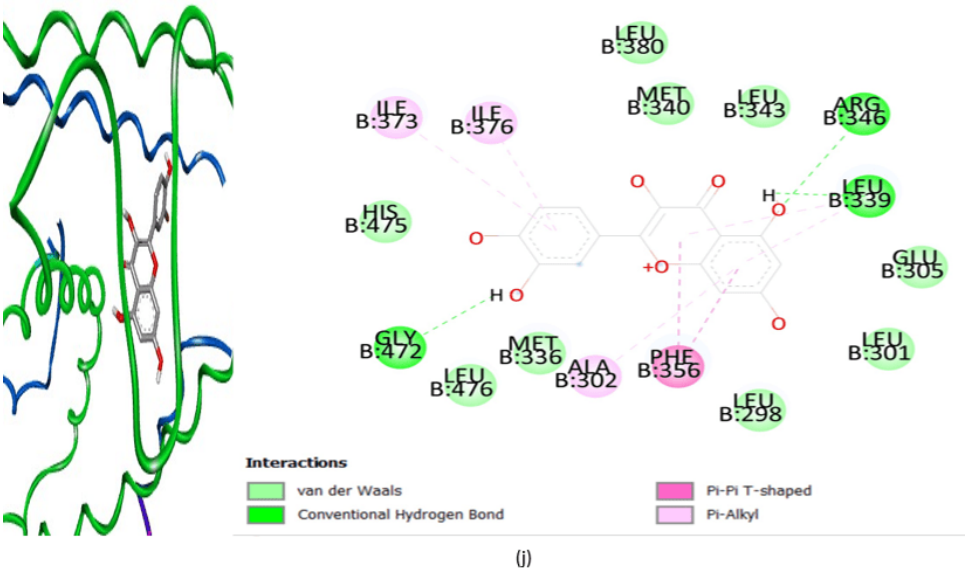


FIGURE 4.37: Analysis of dock complexes of Estrogen Receptor Beta with quercetin

Figure 4.37 shows the interaction of Estrogen Receptor Beta with quercetin. It shows that there are three hydrogen bonds, three alkyl and nine van der waals interactions.

4.12 Lead Compound Identification

The ligands' pharmacokinetic and physiochemical properties determine their fate as for being drug or non-drug compounds. Lipinski's rule is the first filter and pharmacokinetics is the second filter for this identification. All ligands were seen obeying the lipinski rule of five so they all get selected for docking. The next knockout stage is pharmacokinetic screening and docking score. In this screening, hyperoside was selected as it showed the best ADMET values concerning high water solubility, good intestinal absorption, and minimal toxicity. Docking score of hyperoside is good against all receptors. Additionally, hyperoside has a significant quantity of residues having hydrogen bonding and van der waals connections, so hyperoside was selected as the lead compound.

4.13 Reference Anti-cancer Drug Identification

Fluorouracil (5-FU) is chosen as a reference drug because of its multiple uses and efficacy against cancer mechanisms. It is an antimetabolite that works primarily by inhibiting the enzyme thymidylate synthase, which is crucial for DNA synthesis. It gets converted into various active metabolites within the body, which mimic uracil and interfere with the synthesis of thymidine, a building block of DNA. By disrupting the production of thymidine, 5-FU effectively hampers DNA replication and repair in rapidly dividing cancer cells, leading to cell death. Additionally, it can induce misincorporation of its metabolites into RNA, further disrupting cellular processes and contributing to its anticancer effects [156].

4.14 Fluorouracil and Lead Compound Comparison

To identify the better treatment for colon cancer and the best bioactive metabolite for controlling cancer mechanisms, The lead chemical hyperoside and the common

medication fluorouracil were compared. The comparison was being performed through parameters like ADMET properties, lipinski rule and docking complexes analysis.

4.15 Fluorouracil Structure Prediction

First of all fluorouracil structure was downloaded in SDF format from PubChem. Then its energy was minimized by using chem3D pro to get the refined structure. The chemical formula of fluorouracil is $C_4H_3FN_2O_2$ and its refined structure is given in figure 4.38.

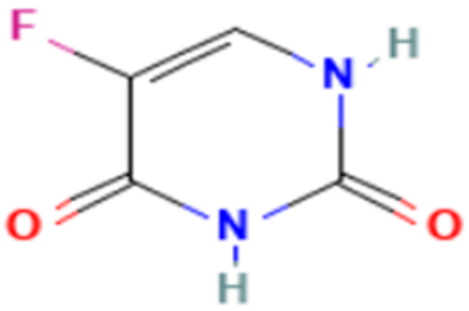


FIGURE 4.38: Structure of fluorouracil

4.16 Lipinski Rule Comparison

The fluorouracil and hyperoside were compared to observe their response to the lipinski rule and to evaluate their pharmacokinetic properties, to assess their bioavailability, safety, efficacy, and drug-likeness. The comparison is given in table 4.11.

TABLE 4.11: The lipinski rule of five comparison

Ligands	**Log P value**	**Molecular weight**	**H-bond donor**	**H-bond acceptor**	**Rotatable bonds**
Fluorouracil	-0.7977	130.078	2	2	0
Hyperoside	-0.5389	464.379	8	10	4

4.17 ADMET Properties Comparison

The ADMET qualities were used to evaluate the drug's and the lead chemical's absorption, distribution, metabolism, excretion, and toxicity to identify a better drug candidate.

4.17.1 The Absorption Properties Comparison

A comparison between fluorouracil and hyperoside for checking absorbance models is given in table 4.12.

TABLE 4.12: Absorption properties comparison

ADMET Properties		**Fluorouracil**	**Hyperoside**
Absorption	Water solubility	-1.555	-2.925
	CaCO2 Permeability	0.559	0.242
	Intestinal absorption(human)	91.698	87.999
	Skin permeability	-3.725	-2.735
	P-glycoprotein substrate	No	No
	P-glycoprotein I inhibitor	No	No
	P-glycoprotein II inhibitor	No	No

Table 4.12 shows that absorption values for both fluorouracil and hyperoside are in range.

Fluorouracil has better water solubility and Caco2 permeability. Both compounds show high intestinal absorption. However, fluorouracil has lower skin permeability making it less likely to penetrate the skin than hyperoside.

Neither drug acts as a substrate or inhibitor for P-glycoprotein, which is favorable for their absorption.

4.17.2 Distribution Properties Comparison

The comparison between the distribution properties of fluorouracil and hyperoside is given in table 4.13.

TABLE 4.13: Distribution properties comparison

ADMET Properties		**Fluorouracil**	**Hyperoside**
Distribution	VDss (human)	-0.23	1.846
	Fraction unbound (human) Fu	0.756	0.228
	BBB permeability log BB	-0.388	-1.688
	CNS permeability log PS	-3.039	-4.093

The above table 4.13 shows the comparative distribution properties of fluorouracil and hyperoside. Fluorouracil has a lower volume of distribution, indicating limited tissue distribution, while hyperoside shows a significantly higher volume, suggesting it spreads more widely in the body. Fluorouracil also has a higher fraction unbound meaning more of it is active in circulation compared to hyperoside, which is more bound to plasma proteins. In terms of blood-brain barriernpermeability and CNS, fluorouracil crosses the BBB and CNS easily than hyperoside.

4.17.3 Metabolism Properties Comparison

The comparison between the metabolism properties of fluorouracil and hyperoside is given in table 4.14.

TABLE 4.14: Metabolic properties comparison

ADMET Properties		**Fluorouracil**	**Hyperoside**
Metabolism	CYP2D6 substrate	No	No
	CYP3A4 substrate	No	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No

Table 4.14 shows that both fluorouracil and hyperoside share similar metabolism profiles, as no compound is a substrate for key cytochrome P450 enzymes, neither drug acts as an inhibitor for these enzymes. This lack of interaction with major metabolic pathways suggests that both fluorouracil and hyperoside may

have a lower risk of drug-drug interactions related to metabolism, making them potentially safer options when used in combination with other medications.

4.17.4 Excretion Properties Comparison

The comparison between the excretion properties of fluorouracil and hyperoside is given in table 4.15.

properly

TABLE 4.15: Excretion properties comparison

ADMET Properties		**Fluorouracil**	**Hyperoside**
Excretion	Total Clearance	0.639	0.494
	Renal OCT2 substrate	No	No

Table 4.15 shows that fluorouracil has a higher total clearance rate compared to hyperoside, indicating that fluorouracil is eliminated from the body more efficiently. Both drugs are not substrates for the renal OCT2 transporter, which suggests they do not rely on this pathway for renal excretion.

4.17.5 Toxicity Properties Comparison

The comparison between the toxicity properties of fluorouracil and hyperoside is given in table 4.16.

TABLE 4.16: Toxicity properties comparison

ADMET Properties		**Fluorouracil**	**Hyperoside**
Toxicity	**AMES toxicity**	**No**	**No**
	Max tolerated dose (human)	1.359	0.569
	hERG I inhibitor	No	No
	hERG II inhibitor	No	No
	Oral rat acute toxicity (LD50)	1.939	2.541
	Oral rat chronic toxicity (LOAEL)	1.587	4.417
	Hepatotoxicity	No	No
	Skin sensitization	No	No

Table 4.16 continued from previous page

ADMET Properties	Fluorouracil	Hyperoside
T.Pyriformis toxicity	-0.236	0.285
Minnow toxicity	3.152	8.061

Table 4.16 shows that fluorouracil and hyperoside have comparable toxicity profiles, as neither drug shows AMES toxicity or hepatotoxicity, and both are not inhibitors of hERG channels. However, fluorouracil has a higher maximum tolerated dose compared to hyperoside, indicating it can be administered at greater levels in humans. In terms of acute toxicity, fluorouracil has a lower oral rat LD50 than hyperoside, suggesting it may be more toxic at higher doses. Conversely, fluorouracil has a lower oral rat chronic toxicity threshold compared to hyperoside, indicating it can cause adverse effects at lower doses over time. Overall both compounds exhibit low toxicity.

4.18 Docking Score Comparison

We docked the lead and standard compounds with the target proteins, aldose reductase, estrogen receptor beta, and carbonic anhydrase 9, then we obtained the binding value from the docking results. The docking score comparison between the lead chemical hyperoside and the conventional medication fluorouracil is displayed in table 4.17.

TABLE 4.17: Docking comparison of fluorouracil and hyperoside

Target Proteins	Ligands	
	Fluorouracil	Hyperoside
Carbonic anhydrase 9	-5.6	-8.2
Aldose reductase	-5.5	-10.5
Estrogen receptor beta	-5.5	-8.9

As can be shown in table 4.17, the vina scores of the lead compound hyperoside are significantly greater than those of the generic medication fluorouracil. The

docking scores of the fluorouracil against target proteins carbonic anhydrase 9, aldose reductase and estrogen receptor beta are -5.6, -5.5 and -5.5 respectively while for hyperoside these scores are -8.2, -10.5 and -8.9 respectively. These results show that lead compound hyperoside can bind with target proteins carbonic anhydrase 9, aldose reductase and estrogen receptor beta more efficiently than the standard drug fluorouracil.

4.19 Docking Analysis Comparison

Depending on the amount of van der Waals, alkyl, and hydrogen bonding, discovery studio evaluated the docking results. The following figures show the docking analysis of fluorouracil.

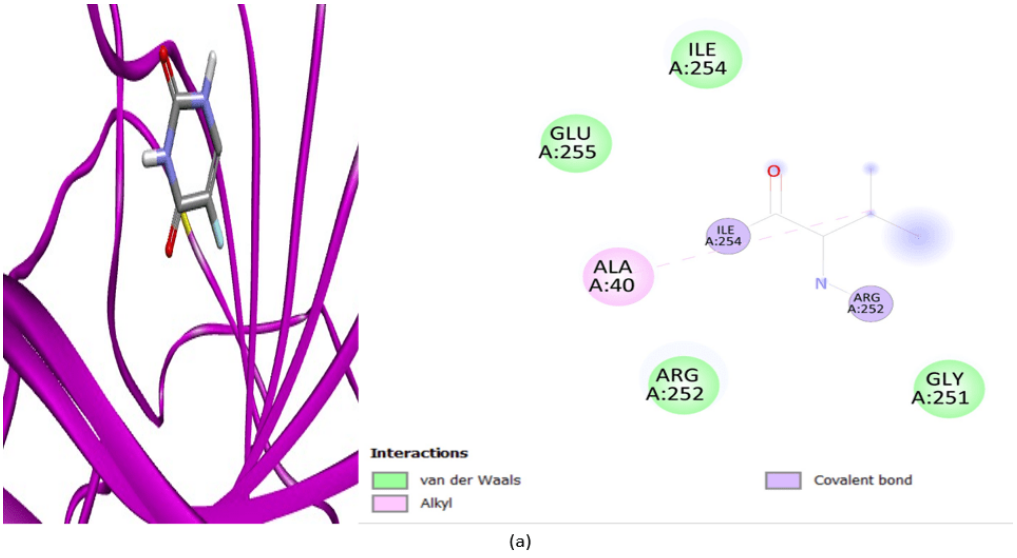


FIGURE 4.39: Docking interaction of carbonic anhydrase 9 with fluorouracil

Figure 4.39 shows the docking interaction of carbonic anhydrase 9 with fluorouracil. It shows that there are two covalent bonds and one alkyl and four van der waals interactions. While in case of interaction of carbonic anhydrase with hyperoside, twelve van der waals contacts and three hydrogen bonds are present. The data demonstrate the hyperoside's strong interaction profle in comparison to fluorouracil.

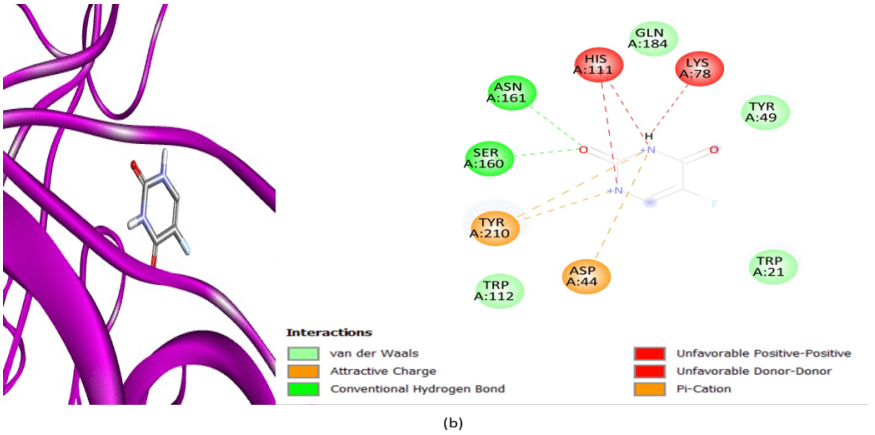


FIGURE 4.40: Docking interaction of aldose reductase with fluorouracil

The docking relationship between fluorouracil and aldose reductase is depicted in Figure 4.40. It shows that there are two hydrogen bonds and four van der waals interactions. There are some unfavourable interactions also. While in case of interaction of aldose reductase with hyperoside, there are three hydrogen bonds and sixteen van der waals connections. Results show strong interaction profile of hyperoside in comparison to fluorouracil.

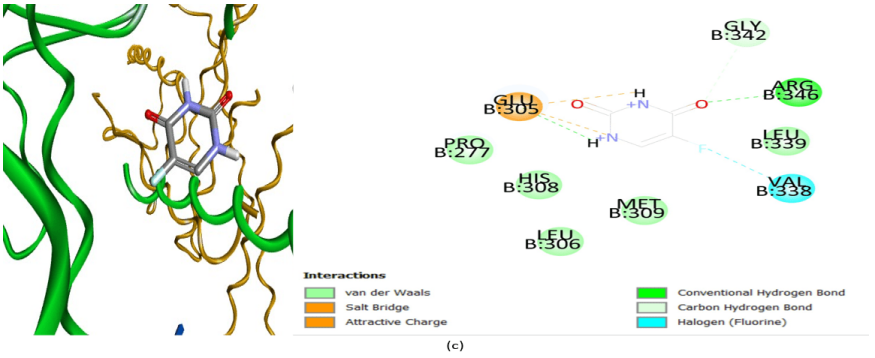


FIGURE 4.41: Docking interaction of estrogen receptor beta with fluorouracil

The docking relationship between fluorouracil and the beta estrogen receptor is depicted in figure 4.41. It demonstrates that there are five van der Waals interactions and one hydrogen bond. In contrast, there is one hydrogen bond, two alkyl, and nine van der Waals contacts when the beta estrogen receptor interacts with the hyperoside. When compared to fluorouracil, the data demonstrate the hyperoside's robust interaction profile.

Overall, the comparison of fluorouracil and hyperoside shows that both share comparable lipinski rules and ADMET analysis. But the docking scores and receptor-ligand interaction profiles of the lead compound hyperoside are better than those of the standard drug, fluorouracil. It shows that hyperoside can act as a promising anti-cancer therapeutic candidate in the context of colon cancer in the future.

Chapter 5

Discussion

The present study investigates the inhibitory potential of Prunus armeniaca metabolites against colon cancer targets through an in-silico approach, integrating molecular docking with ADMET profiling. Being one of the top three most common malignancies diagnosed globally, colon cancer continues to be a serious public health problem [157]. Its multifactorial etiology involves genetic mutations such as those in APC, KRAS, and TP53 epigenetic changes, chronic inflammation, and environmental influences [158]. The limitations of conventional therapies, including significant toxicity, resistance development, and high treatment costs, have intensified the search for safe, affordable, and effective alternatives [159]. In this context, plant-derived bioactives offer unique advantages, including multi-target activity, lower side-effect profiles, and dietary accessibility [160].

Apricots (*P. armeniaca*) are a rich source of flavonoids, phenolic acids, terpenes, vitamins, and minerals, all of which have been implicated in cancer prevention and therapy. Previous research has documented the antioxidant and anti-inflammatory effects of apricot phytochemicals, particularly quercetin, kaempferol, chlorogenic acid, caffeic acid, hyperoside, and β-carotene, which modulate key cancer-related pathways [161]. For instance, quercetin inhibits the NF-κB pathway, thereby reducing inflammation and promoting apoptosis in cancer cells, while chlorogenic acid has been shown to regulate glucose metabolism and angiogenesis in colorectal tumors. Similarly, kaempferol and caffeic acid are known to induce cell cycle arrest,

suppress epithelial-to-mesenchymal transition, and enhance chemotherapy efficacy [162].

In the present docking results, multiple apricot metabolites exhibited strong binding affinities toward colon cancer-related targets—carbonic anhydrase IX, aldose reductase, and estrogen receptor beta. This finding is consistent with previous studies reporting that inhibition of carbonic anhydrase IX disrupts tumor pH regulation, leading to reduced cancer cell survival in hypoxic environments [163]. Similarly, suppression of aldose reductase has been linked to decreased oxidative stress and inflammatory signaling in cancer models. Estrogen receptor beta activation is another promising strategy, as it has been associated with reduced proliferation and enhanced apoptosis in colon epithelial cells. The observed high docking scores of hyperoside, quercetin, and chlorogenic acid toward these proteins provide a molecular rationale for their potential therapeutic use [164].

Importantly, the ADMET analysis in this study revealed favorable pharmacokinetic properties for several metabolites, particularly hyperoside, which showed comparable drug-likeness to the standard chemotherapeutic agent 5-fluorouracil but with a superior docking profile. This aligns with reports that hyperoside exhibits potent antiproliferative activity against colon cancer cells in vitro and possesses good oral bioavailability. Moreover, the multi-target nature of these compounds supports the concept of "polypharmacology" in oncology, where simultaneous modulation of multiple pathways can yield better outcomes and reduce resistance development [140].

The anticancer potential of apricot extracts has also been validated in preclinical models. It was seen that apricot kernel extracts reduced tumor size and oxidative stress markers in murine cancer models. Similarly, amygdalin another apricot-derived compound has shown apoptotic effects in colorectal cancer cell lines, although its toxicity profile requires cautious application. Beyond apricots, related studies on fruit polyphenols such as those from grapes, berries, and green tea have demonstrated inhibition of angiogenesis, induction of autophagy, and modulation of gut microbiota, all relevant to colorectal cancer prevention. This suggests

that apricot metabolites may act synergistically with other dietary compounds to provide a cumulative protective effect [16].

The present study also underscores the importance of integrating computational approaches into early-stage drug discovery. In-silico docking offers rapid, cost-effective screening of natural metabolites before committing to resource-intensive laboratory experiments. This methodology has been successfully applied to identify promising anticancer leads from plant sources, including curcumin analogs, resveratrol derivatives, and epigallocatechin gallate analogs [18]. Our findings add to this growing body of evidence by highlighting hyperoside and quercetin as strong candidates for further in vitro and in vivo validation.

While promising, these results must be interpreted with caution. Docking studies, although predictive, cannot fully account for the complexity of living systems, including metabolic transformations, tissue distribution, and immune modulation. Therefore, future research should involve in vitro cytotoxicity assays, apoptosis detection, and mechanistic pathway analyses, followed by in vivo studies in colorectal cancer models. Additionally, synergistic effects between apricot metabolites and standard chemotherapeutic agents should be explored, as some plant compounds have been shown to sensitize cancer cells to chemotherapy while mitigating side effects. From a public health perspective, dietary incorporation of apricots and other phytochemical-rich fruits aligns with epidemiological data showing reduced colorectal cancer risk among populations consuming high levels of fruits and vegetables. This study confirms and extends previous findings on the anticancer potential of *P. armeniaca* metabolites, offering computational evidence for their strong interactions with colon cancer-related targets and favorable drug-likeness. These results support the further development of apricot-derived compounds as complementary or alternative therapies for colorectal cancer.

Chapter 6

Conclusion and Future Prospects

This research has elucidated the promising anti-cancer properties of bioactive metabolites derived from *Prunus armeniaca*, particularly in relation to colon cancer. The findings indicate that lead compound hyperoside may play a crucial role in inhibiting key pathways involved in tumor progression, thereby opening new avenues for therapeutic applications. The systematic review and in silico analyses conducted in this study have highlighted the potential of compounds such as quercetin, caffeic acid, and other phytochemicals in modulating cancer pathways, suggesting a multifaceted approach to cancer treatment that leverages natural products.

The molecular docking studies revealed significant binding affinities of these metabolites with critical proteins associated with colon cancer, including carbonic anhydrase, aldose reductase, and estrogen receptor beta. These interactions suggest that the metabolites can effectively disrupt the signaling pathways that contribute to cancer progression. These chemicals' advantageous ADMET characteristics further support their potential as safe and effective alternatives to conventional therapies, which often come with severe side effects. Given their bioactive characteristics, these compounds could not only enhance the efficacy of existing treatments but also mitigate the adverse effects associated with them.

The importance of validating these findings through comprehensive in vivo and in vitro studies cannot be overstated. Experimental validation using cellular and

animal models will be vital to confirm the safety and efficacy of these metabolites as potential anti-cancer agents. Knowing the exact molecular processes by which these substances influence the pathways leading to colon cancer will provide deeper insights into their therapeutic potential and could lead to the development of novel treatment strategies. Such research endeavors will not only enhance our understanding of the mechanisms at play but will also pave the way for more targeted therapeutic interventions that can be tailored to individual patient needs [165].

Moreover, exploring the synergistic effects of apricot metabolites with other natural compounds may significantly enhance their anti-cancer efficacy. This approach could lead to the formulation of more potent combinations that capitalize on the strengths of multiple bioactive substances, thereby broadening the scope of natural therapies available for cancer treatment. The interplay between these compounds may create a synergistic effect that optimizes their individual benefits, potentially improving patient outcomes [166].

Clinical trials will be crucial for assessing the safety, efficacy, and optimal dosing of these metabolites in human subjects. The transition from laboratory research to clinical application will help translate these findings into real-world benefits, potentially offering new hope for patients facing the challenges of colon cancer. By establishing a clear link between the laboratory results and clinical outcomes, we can build a stronger case for the integration of these natural compounds into standard treatment protocols [167].

Furthermore, the development of advanced drug delivery systems could improve the bioavailability and targeted action of apricot metabolites, ensuring that these compounds reach their intended sites of action within the body. Techniques such as nanoencapsulation and controlled-release formulations could enhance their therapeutic effects and minimize side effects. By optimizing how these metabolites are delivered, we can maximize their potential benefits while reducing the likelihood of adverse reactions, making them more viable options for patients.

Bibliography

[1] M. Ahmed, "Colon cancer: A clinician's perspective in 2019," *Gastroenterol. Res.*, vol. 13, no. 1, pp. 1–1, 2020.

[2] W. S. Samowitz, "Genetic and epigenetic changes in colon cancer," *Exp. Mol. Pathol.*, vol. 85, no. 1, pp. 64–67, 2008.

[3] L. Laplane, D. Duluc, N. Larmonier, T. Pradeu, and A. Bikfalvi, "The multiple layers of the tumor environment," *Trends Cancer*, vol. 4, no. 12, pp. 802–809, 2018.

[4] V. A. Katzke, R. Kaaks, and T. Kühn, "Lifestyle and cancer risk," *Cancer J.*, vol. 21, no. 2, pp. 104–110, 2015.

[5] World Health Organization, *WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care for All*, Geneva: World Health Organization, 2020.

[6] S. Munker, D. Gerken, M. Banach, C. Stöß, T. F. E. Barth, and M. Mayr, "Chemotherapy for metastatic colon cancer: No effect on survival when the dose is reduced due to side effects," *BMC Cancer*, vol. 18, no. 1, pp. 455–455, 2018.

[7] J. S. Ross, M. Fakih, C. A. Stagnaro-Green, M. Mego, T. J. Lynch, and D. L. Rimm, "Targeted therapies for cancer 2004," *Am. J. Clin. Pathol.*, vol. 122, no. 4, pp. 598–609, 2004.

[8] K. Aravindaram and N.-S. Yang, "Anti-inflammatory plant natural products for cancer therapy," *Planta Med.*, vol. 76, no. 11, pp. 1103–1117, 2010.

[9] C. Bailly, "Anticancer properties of Prunus mume extracts (Chinese plum, Japanese apricot)," *J. Ethnopharmacol.*, vol. 246, pp. 112215–112215, 2020.

[10] D. F. Romagnolo and O. I. Selmin, "Flavonoids and cancer prevention: A review of the evidence," *J. Nutr. Gerontol. Geriatr.*, vol. 31, no. 3, pp. 206–238, 2012.

[11] W. Cassiem and M. de Kock, "The anti-proliferative effect of apricot and peach kernel extracts on human colon cancer cells in vitro," *BMC Complement. Altern. Med.*, vol. 19, no. 1, pp. 32–32, 2019.

[12] Z. Wang, L. Ma, X. Zhang, L. Xu, J. Cao, and W. Jiang, "The effect of exogenous salicylic acid on antioxidant activity, bioactive compounds and antioxidant system in apricot fruit," *Sci. Hortic.*, vol. 181, pp. 113–120, 2015.

[13] L. Gibellini, M. Pinti, M. Nasi, S. De Biasi, E. Roat, L. Bertoncelli, and A. Cossarizza, "Quercetin and cancer chemoprevention," *Evid.-Based Complement. Altern. Med.*, vol. 2011, pp. 591356–591356, 2011.

[14] K. M. M. Espíndola, R. G. Ferreira, L. E. M. Narvaez, A. R. S. Rosario, A. H. M. da Silva, A. G. B. Silva, A. P. O. Vieira, and M. C. Monteiro, "Chemical and pharmacological aspects of caffeic acid and its activity in hepatocarcinoma," *Front. Oncol.*, vol. 9, pp. 541–541, 2019.

[15] I. A. Ansari and M. S. Akhtar, "Current insights on the role of terpenoids as anticancer agents: A perspective on cancer prevention and treatment," in *Natural Bio-active Compounds: Volume 2: Chemistry, Pharmacology and Health Care Practices*, Singapore: Springer, 2019, pp. 53–80.

[16] S. Ali, T. Masud, K. S. Abbasi, T. Mahmood, and A. Hussain, "Apricot: Nutritional potentials and health benefits—A review," *Food Sci. Technol.*, vol. 16, pp. 175–189, 2015.

[17] S. Guruswamy and C. V. Rao, "Multi-target approaches in colon cancer chemoprevention based on systems biology of tumor cell-signaling," *Gene Regul. Syst. Biol.*, vol. 2, pp. 117762500800200005–117762500800200005, 2008.

[18] Q. He, X. Zhang, Y. Yang, Y. Hu, Y. Li, and Y. Zhang, "Exploring the mechanism of curcumin in the treatment of colon cancer based on network pharmacology and molecular docking," *Front. Pharmacol.*, vol. 14, pp. 1102581–1102581, 2023.

[19] S. Pastorekova, M. Zatovicova, and J. Pastorek, "Cancer-associated carbonic anhydrases and their inhibition," *Curr. Pharm. Des.*, vol. 14, no. 7, pp. 685–698, 2008.

[20] R. Tammali, K. V. Ramana, and S. K. Srivastava, "Aldose reductase regulates TNF-α-induced PGE2 production in human colon cancer cells," *Cancer Lett.*, vol. 252, no. 2, pp. 299–306, 2007.

[21] N. Honma, T. Arai, T. Abe, T. Takubo, T. Sato, and Y. Kakugawa, "Estrogen concentration and estrogen receptor-β expression in postmenopausal colon cancer considering patient/tumor background," *J. Cancer Res. Clin. Oncol.*, vol. 148, no. 5, pp. 1063–1071, 2022.

[22] Y. Wang, P. Li, Z. Peng, F. H. She, and L. X. Kong, "Microencapsulation of nanoparticles with enhanced drug loading for pH-sensitive oral drug delivery for the treatment of colon cancer," *J. Appl. Polym. Sci.*, vol. 129, no. 2, pp. 714–720, 2013.

[23] S. Gezici and N. Şekeroğlu, "Current perspectives in the application of medicinal plants against cancer: Novel therapeutic agents," *Anti-Cancer Agents Med. Chem.*, vol. 19, no. 1, pp. 101–111, 2019.

[24] R. Lo Bianco, V. Farina, S. G. Indelicato, F. Filizzola, and P. Agozzino, "Fruit physical, chemical and aromatic attributes of early, intermediate and late apricot cultivars," *J. Sci. Food Agric.*, vol. 90, no. 6, pp. 1008–1019, 2010.

[25] T. Takeda, T. Shimada, K. Nomura, T. Ozaki, T. Haji, M. Yamaguchi, and M. Yoshida, "Classification of apricot varieties by RAPD analysis," *J. Jpn. Soc. Hortic. Sci.*, vol. 67, no. 1, pp. 21–27, 1998.

[26] B. S. Reddy, "Dietary fat and colon cancer: Animal model studies," *Lipids*, vol. 27, no. 10, pp. 807–813, 1992.

[27] E. Gündoğmuş, "Energy use on organic farming: A comparative analysis on organic versus conventional apricot production on small holdings in Turkey," *Energy Convers. Manag.*, vol. 47, no. 18–19, pp. 3351–3359, 2006.

[28] A. R. Rhodes, "Public education and cancer of the skin. What do people need to know about melanoma and nonmelanoma skin cancer?," *Cancer*, vol. 75, no. S2, pp. 613–636, 1995.

[29] Y. Xu, G.-H. Su, D. Ma, Y. Xiao, Z.-M. Shao, and Y.-Z. Jiang, "Technological advances in cancer immunity: From immunogenomics to single-cell analysis and artificial intelligence," *Signal Transduct. Target. Ther.*, vol. 6, no. 1, pp. 312–312, 2021.

[30] M. Hattori, K. Kawakami, M. Akimoto, K. Takenaga, J. Suzumiya, and Y. Honma, "Antitumor effect of Japanese apricot extract (MK615) on human cancer cells in vitro and in vivo through a reactive oxygen species-dependent mechanism," *Tumori J.*, vol. 99, no. 2, pp. 239–248, 2013.

[31] D. Kitic, B. Miladinovic, M. Randjelovic, A. Szopa, J. Sharifi-Rad, D. Calina, and V. Seidel, "Anticancer potential and other pharmacological properties of *Prunus armeniaca* L.: An updated overview," *Plants*, vol. 11, no. 14, pp. 1885–1885, 2022.

[32] G. R. Varadhachary, M. N. Raber, A. Matamoros, and J. L. Abbruzzese, "Carcinoma of unknown primary with a colon-cancer profile—Changing paradigm and emerging definitions," *Lancet Oncol.*, vol. 9, no. 6, pp. 596–599, 2008.

[33] J. B. O'Connell, M. A. Maggard, and C. Y. Ko, "Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging," *J. Natl. Cancer Inst.*, vol. 96, no. 19, pp. 1420–1425, 2004.

[34] I. Soerjomataram and F. Bray, "Planning for tomorrow: Global cancer incidence and the role of prevention 2020–2070," *Nat. Rev. Clin. Oncol.*, vol. 18, no. 10, pp. 663–672, 2021.

[35] S. Saleem, R. Jafri, M. A. Waris, M. E. Malik, A. I. Ansari, and M. A. Khan, "Body mass index and other risk factors effects on colon cancer prognosis in Pakistan," *J. Cancer Allied Spec.*, vol. 8, no. 2, pp. 477–477, 2022.

[36] G. Sandle, "Salt and water absorption in the human colon: A modern appraisal," *Gut*, vol. 43, no. 2, pp. 294–299, 1998.

[37] P. Spratt, C. Nicolella, and D. Pyle, "An engineering model of the human colon," *Food Bioprod. Process.*, vol. 83, no. 2, pp. 147–157, 2005.

[38] M. Chapman, "The role of the colonic flora in maintaining a healthy large bowel mucosa," *Ann. R. Coll. Surg. Engl.*, vol. 83, no. 2, pp. 75–75, 2001.

[39] N. F. G. P. Dias, V. C. Sgarbieri, H. B. Jacobucci, H. A. Rangel, and C. Tanikawa, "Dietary protein, immune function and colon carcinogenesis in the mouse," *Le Lait*, vol. 86, no. 3, pp. 213–226, 2006.

[40] J. M. Piqué, M. Pallarés, E. Cusó, J. Vilar-Bonet, and M. A. Gassull, "Methane production and colon cancer," *Gastroenterology*, vol. 87, no. 3, pp. 601–605, 1984.

[41] J. Torres, S. Mehandru, J.-F. Colombel, and L. Peyrin-Biroulet, "Crohn's disease," *Lancet*, vol. 389, no. 10080, pp. 1741–1755, 2017.

[42] J. D. Feuerstein and A. S. Cheifetz, "Ulcerative colitis: Epidemiology, diagnosis, and management," in *Proc. Mayo Clin.*, vol. 89, no. 11, Rochester, MN: Elsevier, 2014, pp. 1553–1563.

[43] A. Tursi, C. Scarpignato, L. L. Strate, A. Lanas, W. Kruis, A. Lahat, and S. Danese, "Colonic diverticular disease," *Nat. Rev. Dis. Primers*, vol. 6, no. 1, pp. 20–20, 2020.

[44] I. Mármol, C. Sánchez-de-Diego, A. Pradilla Dieste, E. Cerrada, and M. J. Rodriguez Yoldi, "Colorectal carcinoma: A general overview and future perspectives in colorectal cancer," *Int. J. Mol. Sci.*, vol. 18, no. 1, pp. 197–197, 2017.

[45] G. J. Holtmann, A. C. Ford, and N. J. Talley, "Pathophysiology of irritable bowel syndrome," *Lancet Gastroenterol. Hepatol.*, vol. 1, no. 2, pp. 133–146, 2016.

[46] J. F. FitzGerald and L. O. Hernandez III, "Ischemic colitis," *Clin. Colon Rectal Surg.*, vol. 28, no. 2, pp. 93–98, 2015.

[47] S. N. Bonnington and M. D. Rutter, "Surveillance of colonic polyps: Are we getting it right?," *World J. Gastroenterol.*, vol. 22, no. 6, pp. 1925–1925, 2016.

[48] A. Fasano and C. Catassi, "Celiac disease," *N. Engl. J. Med.*, vol. 367, no. 25, pp. 2419–2426, 2012.

[49] D. E. Fry, "Colon preparation and surgical site infection," *Am. J. Surg.*, vol. 202, no. 2, pp. 225–232, 2011.

[50] M. B. Ulanja, M. Rishi, B. D. Beutler, M. Sharma, D. R. Patterson, N. Gullapalli, and S. Ambika, "Colon cancer sidedness, presentation, and survival at different stages," *J. Oncol.*, vol. 2019, pp. 4315032–4315032, 2019.

[51] V. N. Tudyka and S. K. Clark, "Surgical treatment in familial adenomatous polyposis," *Ann. Gastroenterol.*, vol. 25, no. 3, pp. 201–201, 2012.

[52] A. K. Arrington, E. Heinrich, V. Lee, C. Tseng, S. DaCosta, and D. L. Morris, "Prognostic and predictive roles of KRAS mutation in colorectal cancer," *Int. J. Mol. Sci.*, vol. 13, no. 10, pp. 12153–12168, 2012.

[53] A. Malki, R. A. ElRuz, I. Gupta, A. Allouch, S. Vranic, and A.-E. Al Moustafa, "Molecular mechanisms of colon cancer progression and metastasis: Recent insights and advancements," *Int. J. Mol. Sci.*, vol. 22, no. 1, pp. 130–130, 2020.

[54] D. H. Robbins and S. H. Itzkowitz, "The molecular and genetic basis of colon cancer," *Med. Clin.*, vol. 86, no. 6, pp. 1467–1495, 2002.

[55] N. Nakada, T. Mikami, K. Koyama, T. Inoue, K. Okayama, and M. Imoto, "Expression of CA2 and CA9 carbonic anhydrases in ulcerative colitis and

ulcerative colitis-associated colorectal cancer," *Pathol. Int.*, vol. 70, no. 8, pp. 523–532, 2020.

[56] R. Tammali, S. Saxena, A. K. Sharma, S. K. Srivastava, and K. V. Ramana, "Inhibition of aldose reductase prevents colon cancer metastasis," *Carcinogenesis*, vol. 32, no. 8, pp. 1259–1267, 2011.

[57] C. Williams, A. DiLeo, Y. Niv, and J.-Å. Gustafsson, "Estrogen receptor beta as target for colorectal cancer prevention," *Cancer Lett.*, vol. 372, no. 1, pp. 48–56, 2016.

[58] S. M. McCulloch, K. Turnbull, K. L. Lu, E. MacDonald, and J. G. F. Hogge, "The diagnostic value of a change in bowel habit for colorectal cancer within different age groups," *United Eur. Gastroenterol. J.*, vol. 8, no. 2, pp. 211–219, 2020.

[59] L. Hong and N. Ahuja, "DNA methylation biomarkers of stool and blood for early detection of colon cancer," *Genet. Test. Mol. Biomarkers*, vol. 17, no. 5, pp. 401–406, 2013.

[60] K. K. Alexiusdottir, P. Möller, K. Smedh, P. J. Nilbert, and M. Nilbert, "Association of symptoms of colon cancer patients with tumor location and TNM tumor stage," *Scand. J. Gastroenterol.*, vol. 47, no. 7, pp. 795–801, 2012.

[61] Y.-H. Kuo, C.-S. Shi, C. Y. Huang, Y.-C. Huang, and C.-C. Chin, "Prognostic significance of unintentional body weight loss in colon cancer patients," *Mol. Clin. Oncol.*, vol. 8, no. 4, pp. 539–543, 2018.

[62] C. Tofthagen, "Surviving chemotherapy for colon cancer and living with the consequences," *J. Palliat. Med.*, vol. 13, no. 11, pp. 1389–1391, 2010.

[63] K. Mueller, A. A. Karimuddin, C. Metcalf, A. Woo, and S. Lefresne, "Management of malignant rectal pain and tenesmus: A systematic review," *J. Palliat. Med.*, vol. 23, no. 7, pp. 964–971, 2020.

[64] J. D. Vogel, C. Eskicioglu, M. R. Weiser, D. L. Feingold, and S. R. Steele, "The American Society of Colon and Rectal Surgeons clinical practice guidelines

for the treatment of colon cancer," *Dis. Colon Rectum*, vol. 60, no. 10, pp. 999–1017, 2017.

[65] A. Varghese, "Chemotherapy for stage II colon cancer," *Clin. Colon Rectal Surg.*, vol. 28, no. 4, pp. 256–261, 2015.

[66] B. Glimelius, H. Grönberg, J. Järhult, A. Wallgren, and E. Cavallin-Ståhl, "A systematic overview of radiation therapy effects in rectal cancer," *Acta Oncol.*, vol. 42, no. 5–6, pp. 476–492, 2003.

[67] Y.-H. Xie, Y.-X. Chen, and J.-Y. Fang, "Comprehensive review of targeted therapy for colorectal cancer," *Signal Transduct. Target. Ther.*, vol. 5, no. 1, pp. 22–22, 2020.

[68] A. Stein and G. Folprecht, "Immunotherapy of colon cancer," *Oncol. Res. Treat.*, vol. 41, no. 5, pp. 282–285, 2018.

[69] K. Mody and T. Bekaii-Saab, "Clinical trials and progress in metastatic colon cancer," *Surg. Oncol. Clin.*, vol. 27, no. 2, pp. 349–365, 2018.

[70] R. M. Navari, "Nausea and vomiting in advanced cancer," *Curr. Treat. Options Oncol.*, vol. 21, no. 2, pp. 14–14, 2020.

[71] T. G. Smith, C. Clark, E. R. Kessler, J. M. Davies, and S. L. Davis, "Perceptions of patients with breast and colon cancer of the management of cancer-related pain, fatigue, and emotional distress in community oncology," *J. Clin. Oncol.*, vol. 37, no. 19, pp. 1666–1676, 2019.

[72] R. Shah, B. Abraham, J. Hou, and J. Sellin, "Frequency and associated factors of hair loss among patients with inflammatory bowel disease," *World J. Gastroenterol.*, vol. 21, no. 1, pp. 229–229, 2015.

[73] R. Arbuckle, S. Huber, and C. Zacker, "The consequences of diarrhea occurring during chemotherapy for colorectal cancer: A retrospective study," *Oncologist*, vol. 5, no. 3, pp. 250–259, 2000.

[74] L. Panariello, M. Donnarumma, R. V. Iaffaioli, P. Chiodini, M. C. Annunziata, T. Peduto, and G. Fabbrocini, "Skin toxicities during colorectal cancer

chemotherapy: Incidence and pearls of treatment in our experience," *Clin. Colorectal Cancer*, vol. 19, no. 4, pp. e235–e242, 2020.

[75] H. H. Won, J. H. Lee, J. S. Jeong, S. Y. Kim, S. J. Park, and J. K. Kim, "Polymorphic markers associated with severe oxaliplatin-induced, chronic peripheral neuropathy in colon cancer patients," *Cancer*, vol. 118, no. 11, pp. 2828–2836, 2012.

[76] R. Amri, A. M. Dinaux, H. Kunitake, L. G. Bordeianou, and D. L. Berger, "Risk stratification for surgical site infections in colon cancer," *JAMA Surg.*, vol. 152, no. 7, pp. 686–690, 2017.

[77] V. Nasca, M. Barretta, G. Mentrasti, M. B. L. Rocchi, and R. Berardi, "Association of immune-related adverse events with the outcomes of immune checkpoint inhibitors in patients with dMMR/MSI-H metastatic colorectal cancer," *J. Immunother. Cancer*, vol. 11, no. 1, pp. e005493–e005493, 2023.

[78] V. Sun, T. Borneman, M. Koczywas, M. Cristea, B. F. Piper, G. Uman, and B. Ferrell, "Quality of life and barriers to symptom management in colon cancer," *Eur. J. Oncol. Nurs.*, vol. 16, no. 3, pp. 276–280, 2012.

[79] K. J. Emmertsen and S. Laurberg, "Bowel dysfunction after treatment for rectal cancer," *Acta Oncol.*, vol. 47, no. 6, pp. 994–1003, 2008.

[80] J. Sundbøll, S. K. Thygesen, K. Veres, D. Liao, J. Zhao, H. Gregersen, and H. T. Sørensen, "Risk of cancer in patients with constipation," *Clin. Epidemiol.*, vol. 12, pp. 299–310, 2020.

[81] A. Diakun, J. Vignone, B. Miller, S. Sandhu, and J. S. Kwon, "The onset of in-vivo dehydration in gas-based intraperitoneal hyperthermia and its cytotoxic effects on colon cancer cells," *Front. Oncol.*, vol. 12, pp. 927714–927714, 2022.

[82] J. P. Griffin-Sobel, "Symptom management of advanced colorectal cancer," *Surg. Oncol. Clin.*, vol. 15, no. 1, pp. 213–222, 2006.

[83] A. Shinsyu, M. Bito, T. Kokubo, K. Mitsuoka, and S. Yamamoto, "Inflammatory cytokines, appetite-regulating hormones, and energy metabolism in

patients with gastrointestinal cancer," *Oncol. Lett.*, vol. 20, no. 2, pp. 1469–1479, 2020.

[84] M. M. He, Z. C. Zeng, D. Yang, A. J. Butte, and W. C. Hahn, "Circulating liver function markers and colorectal cancer risk: A prospective cohort study in the UK Biobank," *Int. J. Cancer*, vol. 148, no. 8, pp. 1867–1878, 2021.

[85] S. P. Kang and M. W. Saif, "Infusion-related and hypersensitivity reactions of monoclonal antibodies used to treat colorectal cancer—Identification, prevention, and management," *J. Support. Oncol.*, vol. 5, no. 9, pp. 451–457, 2007.

[86] K. Amano, I. Barast, N. Tanizawa, Y. Uno, T. Morita, and T. Maeda, "Significance of fluid retention, body mass index, and weight loss in patients with advanced cancer," *JCSM Clin. Rep.*, vol. 5, no. 3, pp. 69–78, 2020.

[87] J. Vardy, S. B. Chiew, K. Jacobs, C. Brown, and P. Beale, "Cognitive function and fatigue after diagnosis of colorectal cancer," *Ann. Oncol.*, vol. 25, no. 12, pp. 2404–2412, 2014.

[88] A. K. Sikalidis and B. Varamini, "Roles of hormones and signaling molecules in describing the relationship between obesity and colon cancer," *Pathol. Oncol. Res.*, vol. 17, no. 4, pp. 785–790, 2011.

[89] W. I. Fisher, A. K. Johnson, G. R. Elkins, J. L. Otte, D. S. Burns, M. Yu, and J. S. Carpenter, "Risk factors, pathophysiology, and treatment of hot flashes in cancer," *CA Cancer J. Clin.*, vol. 63, no. 3, pp. 167–192, 2013.

[90] L. Liu, J. M. Herrinton, D. L. Hornbrook, J. S. Wendel, and L. H. Kushi, "Second primary cancers in subsites of colon and rectum in patients with previous colorectal cancer," *Dis. Colon Rectum*, vol. 56, no. 2, pp. 158–168, 2013.

[91] M. Li, G. G.-L. Yue, S. K.-W. Tsui, K.-P. Fung, and C. Bik-San Lau, "Turmeric extract, with absorbable curcumin, has potent anti-metastatic effect in vitro and in vivo," *Phytomedicine*, vol. 46, pp. 131–141, 2018.

[92] F. Randisi, G. Perletti, E. Marras, and M. B. Gariboldi, "Green tea components: In vitro and in vivo evidence for their anticancer potential in colon cancer," *Cancers*, vol. 17, no. 4, pp. 623–623, 2025.

[93] P. Su, V. P. Veeraraghavan, S. Krishna Mohan, and W. Lu, "A ginger derivative, zingerone—A phenolic compound—Induces ROS-mediated apoptosis in colon cancer cells (HCT-116)," *J. Biochem. Mol. Toxicol.*, vol. 33, no. 12, pp. e22403–e22403, 2019.

[94] S. A. Emadi, M. G. Rahbardar, S. Mehri, and H. Hosseinzadeh, "A review of therapeutic potentials of milk thistle (Silybum marianum L.) and its main constituent, silymarin, on cancer, and their related patents," *Iran. J. Basic Med. Sci.*, vol. 25, no. 10, pp. 1166–1166, 2022.

[95] C. Peng, Y. Zhang, Y. H. Liu, Y. Zhang, and Y. Zhao, "Study of the aqueous extract of Aloe vera and its two active components on the Wnt/β-catenin and Notch signaling pathways in colorectal cancer cells," *J. Ethnopharmacol.*, vol. 243, pp. 112092–112092, 2019.

[96] H. Bessler and M. Djaldetti, "Broccoli and human health: Immunomodulatory effect of sulforaphane in a model of colon cancer," *Int. J. Food Sci. Nutr.*, vol. 69, no. 8, pp. 946–953, 2018.

[97] E. Y. Seo and W. K. Kim, "Red ginseng extract reduced metastasis of colon cancer cells in vitro and in vivo," *J. Ginseng Res.*, vol. 35, no. 3, pp. 315–315, 2011.

[98] D. Williams, M. Verghese, L. Walker, J. Boateng, L. Shackelford, and C. Chawan, "Flax seed oil and flax seed meal reduce the formation of aberrant crypt foci (ACF) in azoxymethane-induced colon cancer in Fisher 344 male rats," *Food Chem. Toxicol.*, vol. 45, no. 1, pp. 153–159, 2007.

[99] X. Cui, Z. Jin, Q. Li, J. Lin, and Q. Li, "Resveratrol suppresses colitis and colon cancer associated with colitis," *Cancer Prev. Res.*, vol. 3, no. 4, pp. 549–559, 2010.

[100] M. J. Patel, S. Tripathy, K. D. Mukhopadhyay, T. Wangjam, A. B. Cabang, J. Morris, and M. J. Wargovich, "A supercritical CO2 extract of neem leaf (A. indica) and its bioactive liminoid, nimbolide, suppresses colon cancer in pre-clinical models by modulating pro-inflammatory pathways," *Mol. Carcinog.*, vol. 57, no. 9, pp. 1156–1165, 2018.

[101] T. Zhebentyayeva, C. Ledbetter, L. Burgos, and G. Llácer, "Apricot," in *Fruit Breeding*, New York, NY: Springer, 2011, pp. 415–458.

[102] D. Jackson and B. Coombe, "The growth of apricot fruit. I. Morphological changes during development and the effects of various tree factors," *Aust. J. Agric. Res.*, vol. 17, no. 4, pp. 465–477, 1966.

[103] A. A. Wani, Z. A. Dar, A. Kumar, I. Amin, S. Wani, and S. M. Wani, "Assessment of variability in morphological characters of apricot germplasm of Kashmir, India," *Sci. Hortic.*, vol. 225, pp. 630–637, 2017.

[104] S. Z. Hussain, B. Naseer, T. Qadri, T. Fatima, and T. A. Bhat, "Apricots (*Prunus armeniaca*)—Morphology, taxonomy, composition and health benefits," in *Fruits Grown in Highland Regions of the Himalayas: Nutritional and Health Benefits*, Cham: Springer, 2021, pp. 91–102.

[105] S. Malik, R. Chaudhury, O. Dhariwal, and S. Mir, "Genetic diversity and traditional uses of wild apricot (*Prunus armeniaca* L.) in high-altitude north-western Himalayas of India," *Plant Genet. Resour.*, vol. 8, no. 3, pp. 249–257, 2010.

[106] M. H. Al-Soufi, M. H. Al-Zoubi, A. M. Khudr, M. A. Alsheikh, M. Alkurdi, and A. Alkurdi, "A review with updated perspectives on nutritional and therapeutic benefits of apricot and the industrial application of its underutilized parts," *Molecules*, vol. 27, no. 15, pp. 5016–5016, 2022.

[107] D. A. Mohamed, I. Hamed, and S. Mohammed, "Utilization of grape and apricot fruits by-products as cheap source for biologically active compounds for health promotion," *Egypt. J. Chem.*, vol. 64, no. 4, pp. 2037–2045, 2021.

[108] G. Miguel, S. Dandlen, A. Neves, and D. Antunes, "Flavonoids content of different apricot (*Prunus armeniaca* L.) cultivars," in *Proc. WSEAS Int. Conf.*, vol. 10, 2008, pp. 978–1.

[109] Y. Wang, Y. Liu, X. Chen, X. Zhang, and J. Yang, "Chemical profiling and antioxidant activity of Japanese apricot flowers with green sepals: Insights into medicinal potential and harvest optimization," *Ind. Crops Prod.*, vol. 212, pp. 118324–118324, 2024.

[110] C. Garcia-Viguera, P. Bridle, F. Ferreres, and F. A. Tomas-Barberan, "Influence of variety, maturity and processing on phenolic compounds of apricot juices and jams," *Z. Lebensm.-Unters. Forsch.*, vol. 199, no. 6, pp. 433–436, 1994.

[111] G. R. Takeoka, R. A. Flath, T. R. Mon, R. Teranishi, and M. Guentert, "Volatile constituents of apricot (*Prunus armeniaca*)," *J. Agric. Food Chem.*, vol. 38, no. 2, pp. 471–477, 1990.

[112] J. Sochor, M. Skutkova, M. Baron, J. Balik, J. Mlcek, and T. Jurikova, "Content of phenolic compounds and antioxidant capacity in fruits of apricot genotypes," *Molecules*, vol. 15, no. 9, pp. 6285–6305, 2010.

[113] X.-H. Wu, Y.-M. Sun, H.-Y. Liu, and J.-K. Zhang, "Research on aromatic substances in two strains apricot and their parents," *J. Agric. Food Chem.*, vol. unknown, no. unknown, pp. unknown–unknown, 2020.

[114] L. E. Bennett, D. P. Singh, and P. R. Clingeleffer, "Micronutrient mineral and folate content of Australian and imported dried fruit products," *Crit. Rev. Food Sci. Nutr.*, vol. 51, no. 1, pp. 38–49, 2010.

[115] S. Bureau, C. M. Renard, M. Reich, C. Ginies, and J.-M. Audergon, "Change in anthocyanin concentrations in red apricot fruits during ripening," *LWT-Food Sci. Technol.*, vol. 42, no. 1, pp. 372–377, 2009.

[116] L. Yang, J. Liu, J. Wang, Y. Liu, and X. Zhang, "Inhibition of enzymatic browning in freeze-thawed apricot fruit by combined chlorogenic acid and osmotic dehydration treatments," *LWT*, vol. 198, pp. 116066–116066, 2024.

[117] R. Ihns, L. M. Diamante, G. P. Savage, and L. Vanhanen, "Effect of temperature on the drying characteristics, colour, antioxidant and beta-carotene contents of two apricot varieties," *Int. J. Food Sci. Technol.*, vol. 46, no. 2, pp. 275–283, 2011.

[118] F. Karatas and F. Kamışlı, "Variations of vitamins (A, C and E) and MDA in apricots dried in IR and microwave," *J. Food Eng.*, vol. 78, no. 2, pp. 662–668, 2007.

[119] J. Cui, X. Gu, Q. Zhang, Y. Ou, and J. Wang, "Production and anti-diabetic activity of soluble dietary fiber from apricot pulp by Trichoderma viride fermentation," *Food Funct.*, vol. 6, no. 5, pp. 1635–1642, 2015.

[120] G. Durmaz and M. Alpaslan, "Antioxidant properties of roasted apricot (*Prunus armeniaca* L.) kernel," *Food Chem.*, vol. 100, no. 3, pp. 1177–1181, 2007.

[121] M. A. Akhone, A. Bains, M. M. Tosif, P. Chawla, M. Fogarasi, and S. Fogarasi, "Apricot kernel: Bioactivity, characterization, applications, and health attributes," *Foods*, vol. 11, no. 15, pp. 2184–2184, 2022.

[122] S. Sansavini and G. Giannerini, "Advances in apricot growing and management," in *Proc. IX Int. Symp. Apricot Cult.*, vol. 293, 1989, pp. 409–430.

[123] M. Basyony, A. S. Morsy, and Y. A. Soltan, "Extracts of apricot (*Prunus armeniaca*) and peach (Prunus persica) kernels as feed additives: Nutrient digestibility, growth performance, and immunological status of growing rabbits," *Animals*, vol. 13, no. 5, pp. 868–868, 2023.

[124] A. Naryal, S. Acharya, A. K. Bhardwaj, A. Kant, O. Chaurasia, and T. Stobdan, "Altitudinal effect on sugar contents and sugar profiles in dried apricot (*Prunus armeniaca* L.) fruit," *J. Food Compos. Anal.*, vol. 76, pp. 27–32, 2019.

[125] R. Labianca, G. D. Beretta, B. Kildani, L. Milesi, F. Mosconi, and M. A. Pessi, "Colon cancer," *Crit. Rev. Oncol./Hematol.*, vol. 74, no. 2, pp. 106–133, 2010.

[126] W. M. Eldehna, M. A. Salem, T. A. Abdulaziz, S. M. El-Sayed, and M. F. Harras, "Tumor-associated carbonic anhydrase isoform IX and XII inhibitory properties of certain isatin-bearing sulfonamides endowed with in vitro anti-tumor activity towards colon cancer," *Bioorg. Chem.*, vol. 81, pp. 425–432, 2018.

[127] S. K. Burley, H. M. Berman, G. J. Kleywegt, J. L. Markley, H. Nakamura, and S. Velankar, "Protein Data Bank (PDB): The single global macromolecular structure archive," in *Protein Crystallography: Methods and Protocols*, New York, NY: Springer, 2017, pp. 627–641.

[128] A. Roy, A. Kucukural, and Y. Zhang, "I-TASSER: A unified platform for automated protein structure and function prediction," *Nat. Protoc.*, vol. 5, no. 4, pp. 725–738, 2010.

[129] R. Evans, M. O'Neill, A. Pritzel, N. Antropov, A. Senior, and T. Green, "Protein complex prediction with AlphaFold-Multimer," *bioRxiv*, pp. 2021.10.04.463034–2021.10.04.463034, 2021.

[130] S. Pundir, M. Martin, and C. O'Donovan, "UniProt Protein Knowledgebase," in *Protein Bioinformatics: From Protein Modifications and Networks to Proteomics*, New York, NY: Springer, 2017, pp. 41–55.

[131] R. Azimi, M. Ozgul, M. C. Kenney, and B. D. Kuppermann, "Bioinformatic analysis of small humanin like peptides using AlphaFold-2 and Expasy ProtParam," *Invest. Ophthalmol. Vis. Sci.*, vol. 65, no. 7, pp. 1320–1320, 2024.

[132] W. L. DeLano, "PyMOL: An open-source molecular graphics tool," *CCP4 Newsl. Protein Crystallogr.*, vol. 40, no. 1, pp. 82–92, 2002.

[133] M. Punta, P. C. Coggill, R. Y. Eberhardt, J. Mistry, and C. P. Tate, "The Pfam protein families database," *Nucleic Acids Res.*, vol. 40, no. D1, pp. D290–D301, 2012.

[134] A. Volkamer, D. Kuhn, F. Rippmann, and M. Rarey, "DoGSiteScorer: A web server for automatic binding site prediction, analysis and druggability assessment," *Bioinformatics*, vol. 28, no. 15, pp. 2074–2075, 2012.

[135] H. Ghorab, C. Lammi, A. Arnoldi, Z. Kabouche, and G. Aiello, "Proteomic analysis of sweet Algerian apricot kernels (*Prunus armeniaca* L.) by combinatorial peptide ligand libraries and LC-MS/MS," *Food Chem.*, vol. 239, pp. 935–945, 2018.

[136] M. Butkiewicz, E. W. Lowe Jr., R. Mueller, J. L. Mendenhall, P. L. Teixeira, C. D. Weaver, and J. Meiler, "Benchmarking ligand-based virtual high-throughput screening with the PubChem database," *Molecules*, vol. 18, no. 1, pp. 735–756, 2013.

[137] V. K. Narayanaswamy, M. Rissdörfer, and B. Odhav, "Review on CambridgeSoft ChemBioDraw Ultra 13.0 v," *Int. J. Theor. Appl. Sci.*, vol. 5, pp. 45–49, 2013.

[138] J. J. Irwin, "Software review: ChemOffice 2005 Pro by CambridgeSoft," *J. Chem. Inf. Model.*, vol. 45, no. 5, pp. 1461–1462, 2005.

[139] C. A. Lipinski, "Lead- and drug-like compounds: The rule-of-five revolution," *Drug Discov. Today Technol.*, vol. 1, no. 4, pp. 337–341, 2004.

[140] J. C. Dearden, "In silico prediction of ADMET properties: How far have we come?," *Expert Opin. Drug Metab. Toxicol.*, vol. 3, no. 5, pp. 635–639, 2007.

[141] N. S. Pagadala, K. Syed, and J. Tuszynski, "Software for molecular docking: A review," *Biophys. Rev.*, vol. 9, no. 2, pp. 91–102, 2017.

[142] D. A. Gschwend, A. C. Good, and I. D. Kuntz, "Molecular docking towards drug discovery," *J. Mol. Recognit.*, vol. 9, no. 2, pp. 175–186, 1996.

[143] S. S. Pawar and S. H. Rohane, "Review on Discovery Studio: An important tool for molecular docking," *Asian J. Res. Chem.*, vol. 14, no. 1, pp. 81–84, 2021.

[144] D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, and J. R. Grant, "DrugBank: A comprehensive resource for in silico drug discovery and exploration," *Nucleic Acids Res.*, vol. 34, no. suppl_1, pp. D668–D672, 2006.

[145] J. Tibbitts, D. Canter, R. Graff, A. Smith, and L. A. Khawli, "Key factors influencing ADME properties of therapeutic proteins: A need for ADME characterization in drug discovery and development," *mAbs*, vol. 8, no. 2, pp. 229–245, 2016.

[146] H. Van De Waterbeemd, D. A. Smith, K. Beaumont, and D. K. Walker, "Property-based design: Optimization of drug absorption and pharmacokinetics," *J. Med. Chem.*, vol. 44, no. 9, pp. 1313–1333, 2001.

[147] E. Sjögren, H. Thorn, and C. Tannergren, "In silico modeling of gastrointestinal drug absorption: Predictive performance of three physiologically based absorption models," *Mol. Pharm.*, vol. 13, no. 6, pp. 1763–1778, 2016.

[148] T. T. V. Tran, H. Tayara, and K. T. Chong, "Recent studies of artificial intelligence on in silico drug distribution prediction," *Int. J. Mol. Sci.*, vol. 24, no. 3, pp. 1815–1815, 2023.

[149] S. R. Kazmi, R. Jun, M.-S. Yu, C. Jung, and D. Na, "In silico approaches and tools for the prediction of drug metabolism and fate: A review," *Comput. Biol. Med.*, vol. 106, pp. 54–64, 2019.

[150] G. Luo, Z. Yang, M. J. Hageman, A. S. Kalgutkar, and S. K. Balani, "In silico prediction of biliary excretion of drugs in rats based on physicochemical properties," *Drug Metab. Dispos.*, vol. 38, no. 3, pp. 422–430, 2010.

[151] M. D. Segall and C. Barber, "Addressing toxicity risk when designing and selecting compounds in early drug discovery," *Drug Discov. Today*, vol. 19, no. 5, pp. 688–693, 2014.

[152] A. Roncaglioni, A. A. Toropov, A. P. Toropova, and E. Benfenati, "In silico methods to predict drug toxicity," *Curr. Opin. Pharmacol.*, vol. 13, no. 5, pp. 802–806, 2013.

[153] S. Vijayakumar, P. Manogar, S. Prabhu, M. Pugazhenthi, and P. Praseetha, "A pharmacoinformatic approach on Cannabinoid receptor 2 (CB2) and different small molecules: Homology modelling, molecular docking, MD simulations, drug designing and ADME analysis," *Comput. Biol. Chem.*, vol. 78, pp. 95–107, 2019.

[154] S. Durdagi, M. G. Papadopoulos, D. P. Papahatjis, and T. Mavromoustakos, "Combined 3D QSAR and molecular docking studies to reveal novel cannabinoid ligands with optimum binding activity," *Bioorg. Med. Chem. Lett.*, vol. 17, no. 24, pp. 6754–6763, 2007.

[155] U. Baroroh, M. Biotek, Z. S. Muscifa, W. Destiarani, F. G. Rohmatullah, and M. Yusuf, "Molecular interaction analysis and visualization of protein-ligand docking using Biovia Discovery Studio Visualizer," *Indones. J. Comput. Biol.*, vol. 2, no. 1, pp. 22–30, 2023.

[156] R. Labianca, G. D. Beretta, B. Kildani, L. Milesi, F. Mosconi, and M. A. Pessi, "Efficacy of adjuvant fluorouracil and folinic acid in colon cancer," *Lancet*, vol. 345, no. 8955, pp. 939–944, 1995.

[157] E. Dekker, P. J. Tanis, J. Vleugels, P. M. Kasi, and M. Wallace, "Colorectal cancer," *Lancet*, vol. 394, no. 10207, pp. 1467–1480, 2019.

[158] E. R. Fearon, "Molecular genetics of colorectal cancer," *Annu. Rev. Pathol. Mech. Dis.*, vol. 6, no. 1, pp. 479–507, 2011.

[159] D. J. Newman and G. M. Cragg, "Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019," *J. Nat. Prod.*, vol. 83, no. 3, pp. 770–803, 2020.

[160] H. Yuan, Q. Ma, L. Ye, and G. Piao, "The traditional medicine and modern medicine from natural products," *Molecules*, vol. 21, no. 5, pp. 559–559, 2016.

[161] S. Volpe, A. Biasi, C. Saglietti, G. Bosco, and M. Ragusa, "Once-weekly semaglutide induces an early improvement in body composition in patients with type 2 diabetes: A 26-week prospective real-life study," *Nutrients*, vol. 14, no. 12, pp. 2414–2414, 2022.

[162] A. Y. Chen and Y. C. Chen, "A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention," *Food Chem.*, vol. 138, no. 4, pp. 2099–2107, 2013.

[163] M. Y. Mboge, B. P. Mahon, R. McKenna, and S. C. Frost, "Carbonic anhydrases: Role in pH control and cancer," *Metabolites*, vol. 8, no. 1, pp. 19–19, 2018.

[164] A. Carvalho, M. C. Justo, M. C. Henriques, and M. L. Ferreira, "Differential expression of α-2,3-sialyltransferases and α-1,3/4-fucosyltransferases regulates the levels of sialyl Lewis a and sialyl Lewis x in gastrointestinal carcinoma cells," *Int. J. Biochem. Cell Biol.*, vol. 42, no. 1, pp. 80–89, 2010.

[165] S. Rajamanickam and R. Agarwal, "Natural products and colon cancer: Current status and future prospects," *Drug Dev. Res.*, vol. 69, no. 7, pp. 460–471, 2008.

[166] A. Banerjee, S. Pathak, V. D. Subramanium, R. Murugesan, and R. S. Verma, "Strategies for targeted drug delivery in treatment of colon cancer: Current trends and future perspectives," *Drug Discov. Today*, vol. 22, no. 8, pp. 1224–1232, 2017.

[167] T. R. Lannagan, R. Jackstadt, S. J. Leedham, and O. J. Sansom, "Advances in colon cancer research: In vitro and animal models," *Curr. Opin. Genet. Dev.*, vol. 66, pp. 50–56, 2021.