https://doi.org/ 10.33472/AFJBS.6.10.2024.5430-5479

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Natural Compounds Targeting Signaling Pathways in Breast Cancer Therapy

Himanshu Sharma[1*], Prashant Halagali[2], Arnab Majumder[3], Arushi[4], Vijay Sharma[4], Rashmi Pathak[5]

1. Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad (UP)-244001, India
2. Department of Pharmaceutical Quality Assurance, KLE College of Pharmacy, KLE Academy of Higher Education and Research Belagavi, Karnataka, 590001, India
3. Department of Pharmacy; Bharat Pharmaceutical Technology; Amtali, NH-8, Agartala, Tripura (W)-799130
4. Department of Pharmaceutics, Shiva Institute of Pharmacy, Chandpur, Himachal Pradesh, 174004, India
5. Department of Pharmacy, Invertis University, Bareilly (UP)-243123, India

***Corresponding author**
Himanshu Sharma
Teerthankar Mahaveer College of Pharmacy, Teerthankar Mahaveer University, Moradabad- (UP)-244001, India
Email id: amitsharmaaligarh786@gmail.com

Article History

Volume 6,Issue 10, 2024

Received:28 Apr 2024

Accepted : 30 May 2024

doi: 10.33472/AFJBS.6.10.2024.5430-5479

ABSTRACT

Innovative treatment strategies are required for breast cancer, which continues to be a major worldwide health concern. Because of how intricately signaling pathways interact, they are essential targets for cutting-edge treatments. This chapter investigates the possibility of natural substances as therapeutic agents that alter these pathways in treating breast cancer. The chapter starts by providing a summary of the crucial signaling pathways involved in the advancement of breast cancer, including the PI3K/AKT, MAPK, and Wnt/β-catenin pathways. These pathways influence cellular survival, metastasis, and drug resistance, making them prime candidates for therapeutic intervention. Natural substances from different botanical and marine sources have drawn interest for their wide range of bioactive characteristics. The chapter dives into the processes by which these substances affect cells, including kinase inhibition, receptor modification, and apoptosis induction. Their potential to interfere with oncogenic signaling cascades may be seen by carefully examining how they interact with certain pathways. The chapter summarizes preclinical and clinical research examining the effects of natural substances, with a focus on specific signaling pathways. Research shows that they can reduce pathway activation, stop the development of tumors, and make cancer cells more responsive to already available treatments. It also highlights their potential for increased effectiveness and less toxicity to explore synergistic combinations with traditional medicines. A growing field of research is the conversion of natural substances into clinical trials. The chapter offers insights into current studies and discusses potential and obstacles in determining how safe and effective they are for people with breast cancer. By affecting important signaling pathways, natural substances provide a possible route for targeted breast cancer treatment. They provide opportunities for individualized and comprehensive treatment approaches due to their complex processes and possible synergy. To emphasize the significance of responsible resource consumption, ethical issues, and sustainable sourcing are also covered. Integration of natural substances into conventional oncology has a lot of potential for upgrading breast cancer therapy paradigms, provided study and cooperation continue.

Keywords: Breast cancer, PI3K/AKT pathway, Wnt/β-catenin pathway, Cancer treatment

1 Introduction

Millions of people and families worldwide are impacted by breast cancer, making it a serious global health issue.[1] Innovative therapy strategies that focus on the disease's underlying processes are required since it is one of the most common and difficult cancers. The focus of recent research has shifted to natural substances obtained from a variety of sources, including plants and marine creatures, that have the potential to modify signaling pathways linked to the initiation and progression of breast cancer.[2] Abnormal signaling pathways that control important cellular functions are inextricably connected to the etiology of breast cancer. The PI3K/AKT, MAPK, and Wnt/β-catenin cascades, among others, are crucial for controlling cell growth, survival, differentiation, and metastasis.[3] Apoptosis evasion, unchecked proliferation, and the development of invasive characteristics that are unique to cancer cells are all caused by the dysregulation of these pathways .[4] Natural substances are appealing because of their varied bioactive qualities and long history of usage as medicines in many different cultures.[5] They make desirable candidates for targeted therapeutics due to their capacity to interact with certain elements of signaling pathways.[6] These drugs provide an exceptional chance to interfere with carcinogenic signaling networks by blocking important kinases or modifying receptor function .[7] This book chapter sets out on an adventure to investigate the complex interactions between natural substances and signaling pathways in the context of breast cancer. It explores how these substances affect the pathways that fuel the development of cancer. To reveal the promising potential of natural chemicals as supplemental medicinal agents, we will analyze preclinical and clinical trials.[8] The chapter also looks at the potential for synergistic effects when these substances are used with traditional therapies, opening up prospects for improved treatment approaches[9]. A mix of science, tradition, and creativity is encountered when we go further into the world of natural substances that target signaling pathways in breast cancer.[10] This union offers the potential to fundamentally alter the way that breast cancer is treated, taking us one step closer to individualized, all-encompassing strategies that take into account the complex web of disease signals.[11] We want to add to the continuing discussion around the use of nature's pharmacopeia in the battle against breast cancer via this investigation, inspiring optimism for better results and a higher standard of living for people afflicted by this terrible illness.[12]

1.1 Many subtypes of breast cancer

Tumorigenesis begins with ductal hyperproliferation.[13] The development of benign or metastatic cancers may be impacted by several carcinogenic factors divided a variety of molecular kinds of BrCa into the four fundamental categories of breast cancers based on genomic profiling of breast tumors see Figure 1.[14] Gene overexpression often has associations with basal-like and luminal subtypes as well as long and short survival rates.[15]The human epidermal growth factor receptor 2 (HER2) subordinate type, on the other hand, is connected to epidermal growth factor receptor (EGFR) overexpression, and a group of certain genes is likewise connected to a limited lifespan.[16]

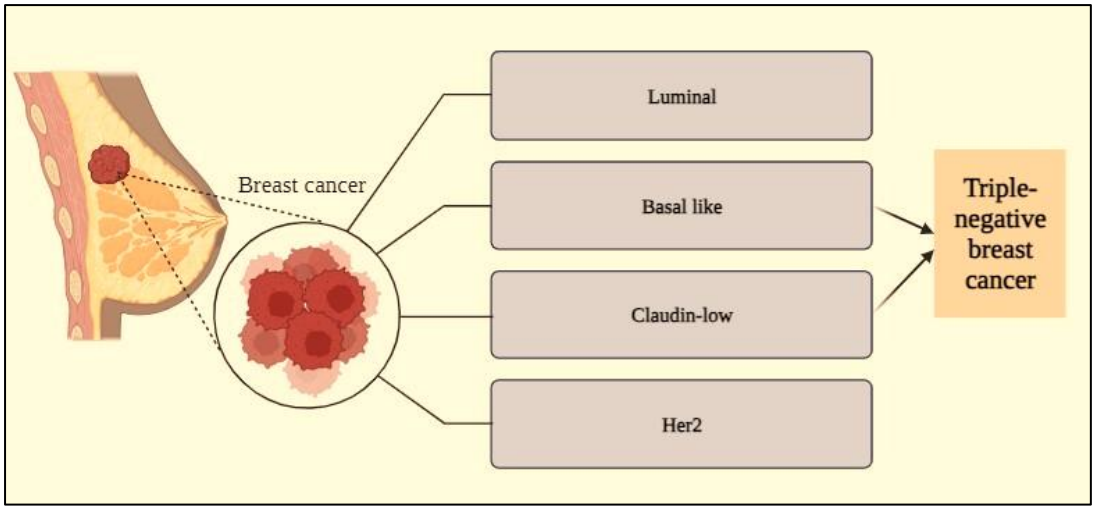

Figure 1. It shows triple breast cancer kinds and molecular subtypes of breast cancer

1.2 Background and significance of breast cancer

The backdrop of the illness, including its incidence, effects, and significance in the medical and social spheres, are referred to as the background and relevance of breast cancer.[17] Breast cancer is a difficult and diverse illness defined by the unchecked expansion of abnormal cells in the breast tissue. Both men and women may get it, although women are far more likely to do so than men.[18] It is one of the most frequent types of cancer in the world. Breast cancer develops as a consequence of genetic abnormalities and changes that interfere with normal cellular control and cause tumors to form.[19] Due to its high incidence rates and severe effects on people, families, and communities, breast cancer is a major problem for the world's health.[20] Its importance may be seen in numerous crucial areas and the most frequent cancer among women diagnosed globally is high frequency breast cancer.[21] It is the main factor in the mortality of women from cancer in several nations.[22] Although early diagnosis and treatment innovations have increased survival rates, breast cancer may still be aggressive and fatal, especially if discovered at an advanced stage.[23] The physical, emotional, and psychological toll that breast cancer may have on people can be quite high.[24] The well-being of patients may be negatively impacted by the adverse effects of treatments including surgery, chemotherapy, radiation, and hormone therapy. Breast cancer's consequences on families, careers, and society as a whole have wide-ranging implications.[25] It may interfere with everyday living, put a strain on finances, and provide emotional difficulties for both sufferers and their loved ones.[26] Our knowledge of cancer biology, genetics, and molecular pathways has significantly improved as a result of advancements in breast cancer research and therapy.[27] As a result, tailored treatment plans and targeted medicines have been developed. Breast cancer awareness initiatives have attracted attention on a worldwide scale, encouraging early identification, access to treatment, and financial research support.[28] Healthcare burden Breast cancer management, diagnosis, and treatment put heavy demands on healthcare systems and resources.[29]

1.3 Role of signaling pathways in cancer development and progression

The emergence and spread of cancer depend heavily on signaling pathways.[30] These pathways are intricate networks of intracellular molecular interactions that control many cellular activities, such as growth, proliferation, survival, differentiation, and death.[31] These pathways

may have a role in the onset and development of cancer when they are dysregulated or disturbed. Here is how signaling pathways affect the development of cancer.[32] In response to external cues, cell growth, and division are induced by unchecked growth and proliferation signaling pathways, such as the PI3K/AKT and MAPK pathways.[33,34] Tumor development in cancer may be caused by mutations or abnormal activation of these mechanisms, which can cause unchecked cell proliferation.[35] A natural process called evasion of apoptosis, or programmed cell death, destroys damaged or defective cells. By skewing the ratio of pro- and anti-apoptotic signals in signaling pathways like the Bcl-2 family, cancer cells often develop the capacity to avoid apoptosis.[36] Signaling mechanisms for angiogenesis and metastasis may encourage the growth of new blood vessels (angiogenesis) and the invasion of cancer cells into nearby tissues as well as the spread of those cells to other locations (metastasis).[37] The routes involved in angiogenesis and metastasis, respectively, include VEGF and MMPs. immunity evasion Some signaling pathways may affect immunological responses, which enables cancer cells to avoid being recognized and eliminated by the immune system.[38] One such example is the ability of the PD-1/PD-L1 axis to inhibit immune surveillance and encourage tumor immune evasion. DNA repair and genomic stability mechanisms, such as the p53 pathway, are essential for preserving the integrity of the genetic material in the cell.[39,40] The accumulation of genetic mutations and the development of cancer may both be caused by the dysregulation of these mechanisms.[41] Signaling pathways controlled by hormones (such as estrogen and androgen) may affect the development and progression of tumors in hormone-dependent malignancies, such as breast and prostate cancer.[42] Signaling pathways often engage in cross-talk and feedback loops, resulting in the formation of intricate networks that either amplify or attenuate messages.[43]An further factor in the development of cancer is dysregulation of one system, which might have unexpected consequences on other pathways.[44]

1.4 The rationale for exploring natural compounds as potential therapeutic agents

Several strong reasons are behind the investigation of natural substances as possible medicinal agents. Due to their wide range of bioactive qualities and potential to treat several illnesses, including cancer, these natural chemicals, which are produced from plants, marine creatures, and other natural sources, have drawn interest.[45] Natural chemicals' diverse chemical structures are one of the justifications for researching them as medicinal agents.[46] A wide variety of chemical structures and characteristics are present in natural substances.[47] Due to their ability to interact with a variety of cellular targets and signaling pathways, these prospective drug candidates may have a broad range of therapeutic effects.[48] This diversity makes them a rich source of possible drug candidates.[49] Cultural and historical use For their health advantages, natural ingredients from folk cures and herbal medicines have been employed by several civilizations throughout history.[50] These antiquated methods serve as a significant resource for current research projects and provide light on prospective therapeutic uses. many different ways that something works Multiple cellular functions are often impacted at once by natural substances' diverse modes of action.[51] Due to their adaptability, they may focus on several disease-related processes, including angiogenesis, apoptosis, inflammation, and proliferation. Possibilities of tailored treatment Specific signaling pathways or molecular targets that are dysregulated in illnesses like cancer have been demonstrated to be susceptible to being targeted by some natural substances.[52] When compared to traditional treatments, this selectivity may

result in therapies that are more targeted and have fewer off-target effects. Natural substances may be used in conjunction with current medications to improve their effectiveness, lessen negative effects, or get around resistance mechanisms.[53] The interaction of natural substances with established treatments has the potential to enhance patient outcomes. security profile Since many natural substances have been ingested as part of the human diet for many generations, it is likely that they have a pretty good safety profile.[54] This gives us a solid base from which we may reasonably confidently explore their therapeutic potential.[55] Natural chemicals may act as skeletons for the construction of new therapeutic leads. Researchers can enhance their pharmacological effects by changing their chemical structures, perhaps producing more effective molecules and selective ones.[56] The discovery of natural substances encourages the preservation of biodiversity as scientists examine diverse plant and marine species to find potentially useful bioactive chemicals.[57] Ecological and moral issues are in line with this emphasis on sustainable sources.[58] The various modes of action of natural compounds and their interactions with different genetic profiles point to possible uses in personalized medicine.[59] The efficacy of therapy may be improved by treating patients according to their unique molecular profile.[60] Affordable and available resources Compared to synthetic chemical libraries, natural chemicals may provide more affordable options for medication discovery and development. This may result in the development of accessible, inexpensive medicines for a larger population.[61]

2 Key signaling pathways in breast cancer

A variety of signaling pathways that regulate essential cellular functions are dysregulated in breast cancer, which is a diverse illness. Understanding the processes behind breast cancer formation, progression, and therapy responses is made possible by the molecular complexity of these pathways.[62] This section focuses on two essential signaling pathways PI3K/AKT and MAPK and their importance in the pathophysiology of breast cancer.[63] The pathway of PI3K and AKT. Cell growth, survival, and metabolism are all heavily dependent on the PI3K/AKT pathway.[64] A cascade that eventually results in the phosphorylation and activation of AKT, a serine/threonine kinase, is set off by the PI3K enzyme being activated. By preventing apoptosis, activated AKT encourages cell survival.[65] It also speeds up cell cycle progression and increases protein synthesis. PI3K/AKT pathway dysregulation is common in breast cancer.[66] Genetic changes in this pathway's constituent parts, such as PIK3CA mutations, PTEN loss, and AKT gene amplification, are rather prevalent. Uncontrolled cell proliferation, apoptosis resistance, and an elevated risk of metastasis are all caused by PI3K/AKT hyperactivation.[67]A network of kinases called the MAPK pathway transmits extracellular signals to the nucleus, affecting gene expression and cellular reactions. c-Jun N-terminal kinase JNK, ERK, and p38 MAPK are the three main branches of the pathway.[68] Particularly ERK is connected to cell growth, differentiation, and survival. Tumor development and progression in breast cancer are attributed to deregulation of the MAPK pathway.[69] Angiogenesis, unchecked cell division, and metastasis may all be caused by the aberrant activation of this pathway, which often results from upstream receptor tyrosine kinase activation[70]

2.1 Importance of these pathways in breast cancer pathogenesis

With their contributions to many aspects of tumor growth, progression, and treatment response, the PI3K/AKT and MAPK signaling pathways play crucial roles in the pathogenesis of breast cancer.[71]When they are dysregulated, a series of things might happen that encourage the development, survival, and metastasis of the tumor.[72]It is possible to identify treatment targets and tactics by comprehending the relevance of these pathways in breast cancer.[73] PI3K/AKT pathway tumor cell survival and resistance to apoptosis Hyperactivation of the PI3K/AKT pathway makes it possible for cancer cells to avoid apoptosis, a process that destroys aberrant cells by programmed cell death.[74] A tumor's ability to develop is facilitated by the ability of cancer cells to survive and proliferate. Cell cycle progression and cellular growth are induced by cell proliferation and expansion of the PI3K/AKT pathway.[75] When this system is dysregulated, tumors may develop as a consequence of unchecked cell division. EMT, a process that improves cancer cell motility and invasion key actions in metastasis is promoted by the activation of PI3K/AKT during metastasis and invasion.[76] The angiogenesis process, which promotes the development of new blood vessel-feeding tumors, may also be influenced by this route. resistance to treatment Hyperactivation of PI3K/AKT has been linked to resistance to several treatments, particularly hormonal ones.[77] By focusing on this route, it may be possible to overcome treatment resistance and improve therapeutic effectiveness. MAPK pathway cell expansion and proliferation.[78] Cell proliferation and growth are mostly regulated by the MAPK pathway, namely the ERK branch.[79] Unnatural cell division brought on by abnormal activation may aid in the development and spread of tumors.[80] The MAPK pathway may be activated during invasion and metastasis to increase the motility and invasion of cancer cells and aid in the spread of metastatic disease.[81] Additionally, it supports the growth of tumors in distant areas by assisting in the development of new blood vessels.[82] Cell survival may be impacted by the modulation of apoptosis regulators caused by resistance to apoptosis in the MAPK pathway.[83] Cancer cells can avoid programmed cell death when this pathway is dysregulated, which lowers the rate of apoptosis.[84] Therapeutic MAPK pathway activation may impart resistance to a range of medications, including targeted therapy. Inhibiting this mechanism could make cancer cells more receptive to medical treatments.[85]

2.2 Interconnections and crosstalk among pathways

The complex interactions and crosstalk across signaling pathways have a role in the development of breast cancer. These interactions build a dynamic network that influences the growth, spread, and effectiveness of treatments for tumors.[86] The interactions between pathways influence how cancer cells behave by enhancing or attenuating the impact of particular pathways.[87] To develop successful treatment plans, it is essential to comprehend these linkages. PI3K/AKT and MAPK pathway crosstalk PI3K/AKT and MAPK pathways typically display crosstalk in breast cancer.[88] AKT activation may promote the production of growth factors and receptors that feed into the MAPK pathway, increasing cell survival and proliferation. On the other hand, MAPK pathway activation may increase AKT, encouraging cell survival and apoptosis resistance.[89] By amplifying oncogenic signaling, this bidirectional interaction promotes tumor development and therapy resistance.[90] The PI3K/AKT pathway also interacts with the mTOR system, which regulates protein synthesis and cell proliferation, in a process known as PI3K/AKT-MTOR crosstalk.[91] AKT turns on mTOR, which controls protein synthesis and cellular metabolism.[92] Uncontrolled cell growth and tumor development

may result from the dysregulation of this connection.[93] The epithelial-mesenchymal transition (EMT) process may interact with the wnt/-catenin pathway, which is important in cell proliferation and differentiation.[94] Enhancing cell motility and invasiveness via EMT is essential for metastasis.[95] EMT may be induced by activation of the Wnt/-catenin pathway, which encourages tumor cell invasion and migration.[96] Signaling pathways and hormone receptors, such as the human epidermal growth factor receptor 2 (HER2) and the estrogen receptor (ER), often interact. As an example, whereas HER2 activation may promote the MAPK pathway, ER signaling can also activate PI3K/AKT.[97] These crosstalk systems help hormone-dependent breast tumors spread. Immune signaling interacts with inflammatory pathways, and it also does so with cancer-related pathways. Immune responses and immune cell infiltration may be influenced by elements of the MAPK and PI3K/AKT pathways in the tumor microenvironment.[98]

3 Natural compounds and their mechanisms of breast cancer

The ability of natural substances to affect breast cancer signaling pathways has drawn attention from a variety of sources, including plants, marine creatures, and conventional medicines. These substances include bioactive elements that interact with certain molecular targets to modulate vital cellular functions implicated in the initiation and spread of cancer.[99] Many natural substances work by attaching to cell surface receptors to modulate their effects. As an example, flavonoids, which are compounds present in certain plants, may interact with estrogen receptors and alter hormonal signaling in breast tumors that express hormone receptors.[100] Changes in gene expression and a decrease in the growth of cancer cells may result from this modulation. Kinase inhibition natural substances can inhibit kinases, which may affect signaling cascades.[101] Resveratrol and curcumin are examples of polyphenols that inhibit kinases in the PI3K/AKT and MAPK pathways.[102] This prevents oncogenic activation and encourages cell cycle arrest or death. Natural substances can start apoptotic pathways in cancer cells.[103] The activation of pro-apoptotic proteins and the downregulation of anti-apoptotic factors by substances like curcumin and green tea catechins results in the death of cancer cells.[104] Some natural substances have anti-inflammatory qualities, and inflammation has been related to the development of cancer.[105] For instance, resveratrol blocks the production of inflammatory cytokines and molecules, possibly lowering the pro-inflammatory milieu that promotes the formation of cancer.[106] Natural substances can affect epigenetic alterations, influencing gene expression without changing the DNA sequence. By controlling DNA methylation and histone changes, they may be able to silence oncogenes or reactivate tumor suppressor genes. adverse impact on angiogenesis.[107] The growth of tumors depends on angiogenesis, the development of new blood vessels. Vascular endothelial growth factor (VEGF) and other angiogenesis-related molecules are the targets of natural substances like curcumin and epigallocatechin gallate (EGCG), which suppress angiogenesis.[108] Cancers that rely on hormones may be affected by some natural substances that imitate or compete with hormones.[109] Soy and other plants contain phytoestrogens, which may bind to estrogen receptors and perhaps modify pathways involved in hormone production.[110] Cancer development is influenced by antioxidant activity and oxidative stress. Vitamins C and E and other naturally occurring substances with antioxidant characteristics may reduce DNA damage and prevent tumor development by scavenging reactive oxygen species. At certain stages of

the cell cycle, natural chemicals that regulate the cell cycle may stop the growth of cancer cells. For example, substances like paclitaxel extracted from the pacific yew tree disrupt microtubule dynamics, causing cell cycle arrest and cell death Figure 2.[111]

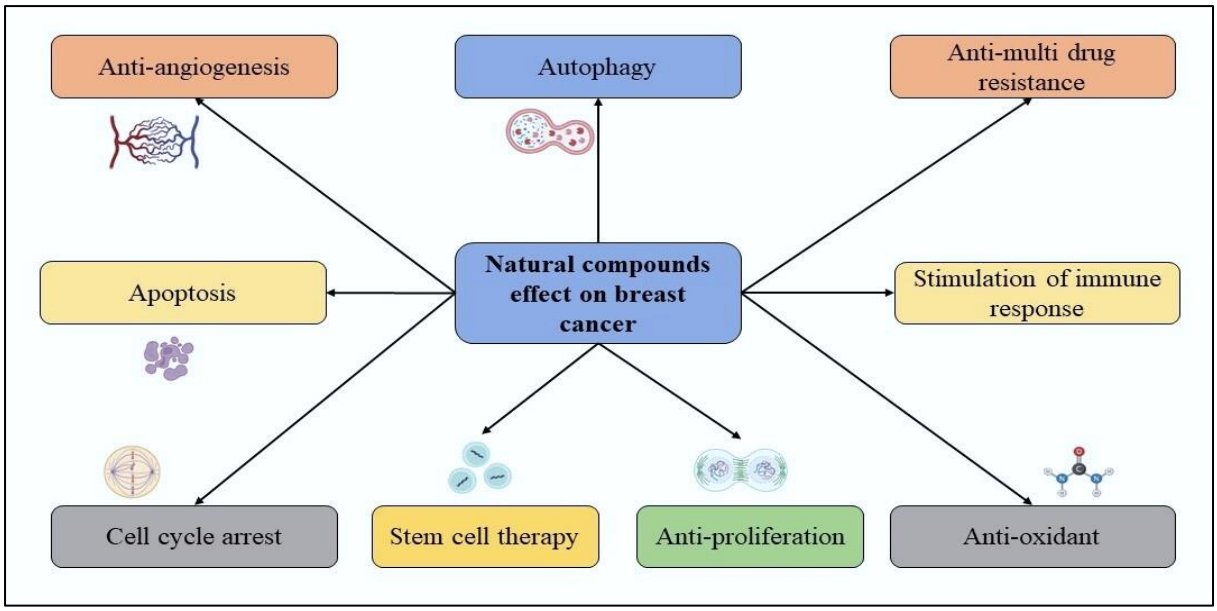

Figure 2. Impact of natural substances on breast cancer with several functions

3.1 Introduction to natural compounds and their sources

Natural substances have drawn the interest of academics and clinicians alike because of their potential therapeutic characteristics. These substances may be obtained from a wide variety of plant, marine, and microbial sources. These substances, which often include bioactive chemicals, provide an abundance of opportunities for cutting-edge therapies and interventions for a wide range of disorders, including breast cancer. origins in plants for millennia, plants have been used as a traditional source of natural substances.[112] A wide variety of bioactive compounds are found in the leaves, stems, roots, and fruits of plants, among other plant parts. Plants produce these substances to protect themselves from environmental stresses and predators.[113] Natural substances originating from plants have been used for their therapeutic capabilities in herbal medicines, traditional healing systems including traditional Chinese medicine, and indigenous knowledge.[114] seafood resources A mostly untapped frontier of natural substances is the ocean. Algae, sponges, corals, and mollusks are a few examples of marine species that are abundant producers of unusual bioactive chemicals. The maritime environment, with its harsh circumstances and varied ecosystems, promotes the creation of substances with unique structures and powerful biological activity.[115] Intriguing prospects for cancer treatment, marine natural chemicals have shown promise in reducing cancer cell proliferation and angiogenesis.[116] Natural chemicals are produced in large quantities by a wide variety of microorganisms, such as bacteria and fungi. Microbial sources are the source of many antibiotics and immunosuppressants.[117] The immense potential of microbial genomes for the synthesis of many bioactive compounds has been shown by recent advances in genome sequencing. Natural substances produced by microorganisms show potential as targeted treatments for many disorders, including cancer.[118] The discovery of several natural substances with therapeutic characteristics is a result of both conventional wisdom and contemporary

study on ethnobotanical knowledge, traditional medical systems, and indigenous traditions.[119] These ancient usages often serve as the basis for contemporary scientific research. Validating the effectiveness and safety of natural chemicals for medicinal reasons requires rigorous research techniques, such as phytochemical analysis, bioassays, and clinical trials. There are several difficulties and possibilities for natural chemicals.[120] It may take a lot of work and sophisticated technology to isolate and characterize bioactive compounds from intricate natural sources. Another issue is ensuring the uniform quality, standardization, and safety of natural chemicals for therapeutic application. The ecological effects of overharvesting and unsustainable methods also raise moral questions.[121]

3.2 Mechanisms by which natural compounds influence signaling pathways

When interacting with signaling pathways in breast cancer cells, natural substances use a variety of strategies. They can alter important molecular processes involved in the initiation and progression of cancer via these pathways.[122] Utilizing the medicinal potential of natural chemicals requires an understanding of how they act on signaling pathways. Modulation and receptor binding.[123] Natural substances can bind to cell surface receptors directly, changing the activity of the receptors and the signaling that follows. For example, phytoestrogens in soy bind to estrogen receptors and affect hormonal signaling in hormone-dependent breast tumors.[124] Gene expression and cellular reactions may be affected by this regulation. Some naturally occurring substances can inhibit kinases. They may hinder the action of kinases, which modify proteins by adding phosphate groups to control signaling pathways.[125] Natural chemicals disrupt oncogenic signaling and reduce the development of cancer cells by inhibiting important kinases in pathways including PI3K/AKT and MAPK.[126] Natural substances can cause apoptosis, or programmed cell death, in cancer cells. They do this by causing the death of cancer cells by activating pro-apoptotic proteins and blocking anti-apoptotic factors. These drugs often target proteins in the Bcl-2 family, which control apoptosis. Changing the epigenome Certain natural substances have an impact on epigenetic changes that regulate gene expression without changing DNA sequences. They can control DNA methylation and histone changes, possibly suppressing oncogenes or reactivating tumor suppressor genes, which helps control the growth of cancer cells. adverse impact on angiogenesis.[127] The growth of new blood vessels that feed tumors, or angiogenesis, may be inhibited by natural substances. These drugs interfere with the angiogenic process, inhibiting tumor development and metastasis by targeting molecules like vascular endothelial growth factor (VEGF).[128] Cancer development and inflammation control are related, and several natural substances have anti-inflammatory characteristics. They may result in an environment that is less favorable for the development and survival of cancer because they may suppress cytokines and inflammatory chemicals.[129] Regulation of oxidative stress Natural substances having antioxidant characteristics displace reactive oxygen species, lowering oxidative stress and DNA deterioration.[130] These substances may prevent cancer from starting and spreading by encouraging a less hostile cellular environment. Cell cycle arrests Natural substances may disrupt the cell cycle, stopping cancer cells at certain stages. For instance, marine-derived substances may alter microtubule dynamics, causing cell cycle arrest and death.[131] Natural substances that regulate hormones may imitate or compete with hormones, affecting hormone-related pathways in malignancies

that are hormone-dependent. This may affect how these tumors develop and respond cellularly.[132]

3.3 Receptor binding, enzyme modulation, and downstream effects

Natural substances have a variety of methods by which they impact the development of breast cancer. Receptor binding and enzyme modulation are two of these processes that are crucial in determining the outcomes of signaling pathways.[133] These interactions play a crucial role in blocking oncogenic signaling and providing possible treatments. The estrogen receptors ER, PR, and AR are only a few examples of natural substances that may interact with hormone receptors.[134] Plant-based phytoestrogens, for instance, can bind to ER and affect estrogen signaling. This interaction may result in the competitive suppression of endogenous hormones in hormone receptor-positive breast tumors, perhaps inhibiting the proliferation of cancer cells. RTKs, or receptor tyrosine kinase receptors, are key players in the development of cancer.[135] By attaching to RTKs' extracellular domains, natural substances may prevent them from activating. [136] For instance, substances in green tea can bind to the EGFR, which inhibits downstream signaling and decreases cell proliferation. Natural substances can block kinases, enzymes that control signaling pathways by adding phosphate groups to proteins.[137] The phosphorylation events that set off subsequent signaling cascades are interfered with by this interference.[138] Curcumin, for instance, blocks many kinases in the PI3K/AKT and MAPK pathways, reducing their carcinogenic effects. activation of enzymes on the other hand, certain natural substances activate enzymes that block processes that cause cancer.[139] The antioxidant resveratrol, which is present in red grapes, may activate sirtuins that support DNA repair and cell cycle control, possibly reducing the development of tumors.[140] By affecting cyclins, cyclin-dependent kinases (CDKs), and cell cycle inhibitors, natural substances often affect the advancement of the cell cycle. Compounds like paclitaxel prevent the division of cancer cells by causing cell cycle arrest, which slows the development of tumors.[141] Natural substances that alter apoptotic pathways cause apoptosis to occur. They may cause caspase activation, upregulate pro-apoptotic proteins, downregulate anti-apoptotic elements, and cause cancer cell death. Matrix metalloproteinases (MMPs), which promote the migration of cancer cells, are one example of a chemical that inhibits metastasis.[142] Natural substances like curcumin may reduce breast cancer cells' capacity for invasion and metastasis by blocking MMPs. regulating angiogenesis Targeting molecules like vascular endothelial growth factor (VEGF) allows natural substances to have an impact on angiogenesis.[143] These substances prevent the development of new blood vessels by blocking VEGF, which slows the growth and spread of tumors. Gene expression controls Natural substances can modify gene expression via epigenetic processes. They modify histone modifications and DNA methylation, possibly suppressing oncogenes and reactivating tumor suppressor genes.[144]

4 PI3K/AKT pathway targeting

Cell growth, survival, metabolism, and proliferation are all controlled by the PI3K/AKT signaling system. The common dysregulation of this system in breast cancer contributes to tumor development, growth, and treatment resistance.[145] A promising approach for treating breast cancer is to target the PI3K/AKT pathway, and natural substances may provide ways to become involved. The activation of the process may be interfered with by inhibiting PI3K's

essential enzyme components. [146] Natural substances like quercetin and resveratrol have been shown to suppress PI3K activity, attenuating downstream signaling and impeding the development of cancer cells.[147] In breast cancer, AKT, a crucial component of the system, is often hyperactivated. Resveratrol, curcumin, and EGCG (green tea catechin) are examples of natural substances that may block AKT activation and hence reduce cell survival and proliferation. Following AKT, mTOR Targeting regulates protein synthesis and cell growth.[148] Natural substances like rapamycin and its derivatives may block mTOR activity, which reduces the growth of cancer cells. Loss of PTEN, a tumor suppressor that blocks PI3K activity, is typical in breast cancer. [149]PTEN's regulatory function in the PI3K/AKT pathway may be restored by several natural substances, such as genistein and curcumin. Natural substances used in synergistic combinations may work in conjunction with treatments that target the PI3K/AKT pathway. For instance, mixing PI3K inhibitors with organic substances like curcumin or resveratrol may improve therapeutic effectiveness and get around resistance mechanisms. Resistance to treatment is often attributed to the PI3K/AKT pathway. By altering the route, natural substances may make resistant breast cancer cells susceptible to conventional therapies.[150] By blocking AKT, EGCG, for instance, may improve the effects of chemotherapy. Despite the PI3K/AKT pathway's critical functions in typical cellular activities, possible adverse effects are raised despite the pathway's prospective targets. Natural chemicals may allow for more precise treatments with less hazardous side effects due to their selective targeting and capacity to influence a variety of pathway components.[151,152,153]

4.1 Examination of natural compounds targeting the PI3K/AKT pathway

Natural substances from a variety of sources have drawn interest because of their potential to block the PI3K/AKT signaling pathway in breast cancer. These drugs provide a novel strategy for controlling this pathway's aberrant activation, which is essential for the initiation and progression of cancer.[154] Here, we explore various natural substances that may be effective in blocking the PI3K/AKT pathway in breast cancer. Inhibitory effects on the PI3K/AKT pathway have been shown in breast cancer cells by curcumin, a medicinal component of turmeric.[155] Cell survival, proliferation, and invasion may be reduced as a result of suppressing AKT activity. A powerful contender for reducing oncogenic signaling, curcumin's multitargeted strategy also entails blocking downstream AKT effectors including mTOR and NF-B. It has been shown that resveratrol, which is prevalent in red grapes and certain berries, prevents PI3K/AKT pathway activation. It affects the pathway's PI3K, AKT, and mTOR among other elements.**[156]** Resveratrol's potential as a natural substance with many effects is shown by its activities, which include decreased cell viability, enhanced apoptosis, and hindered cancer cell migration. In breast cancer cells, EGCG (Epigallocatechin Gallate), the main catechin in green tea, demonstrates AKT-inhibitory activities. AKT activation may result in reduced cell growth and increased susceptibility to chemotherapy, which is what EGCG inhibits.[157] The potential of EGCG to target the PI3K/AKT pathway and prevent cancer cell survival is further aided by its antioxidant capabilities. Various fruits and vegetables include the flavonoid quercetin, which can block the PI3K/AKT pathway in breast cancer cells. Cell cycle arrest and apoptosis are caused by the suppression of PI3K activity and downstream AKT signaling.[158] The ability of quercetin to inhibit tumor development and spread is further enhanced by its anti-angiogenic properties. Genistein, which is included in soy products, can influence many steps in the

PI3K/AKT pathway.[159] It stops PTEN expression from being lost in breast cancer cells, reduces AKT signaling and prevents PI3K activation. Genistein's capacity to inhibit cell growth and trigger apoptosis is a result of this multimodal strategy.[160] The interaction between natural substances that target the PI3K/AKT pathway and conventional medicines has been studied in conjunction with several other investigations. Natural substances like curcumin, resveratrol, or EGCG may improve treatment results and circumvent resistance mechanisms when used with chemotherapy or targeted medicines.[161]

4.2 Discussion of specific compounds and their effects

Breast cancer has been shown to respond differently to curcumin, a substance derived from the turmeric plant.[162] By preventing the activation of PI3K and AKT, it blocks PI3K/AKT signaling. Cell cycle arrest, the activation of apoptosis, and a reduction in cancer cell migration are all results of this interference.[163] The anti-inflammatory and antioxidant characteristics of curcumin further increase its potential as an additional therapy in the treatment of breast cancer. Red grapes and several berries contain resveratrol, which has shown potential for treating breast cancer. It interferes with PI3K/AKT activation, which reduces the growth and survival of cancer cells. Additionally, resveratrol increases the susceptibility of breast cancer cells to chemotherapy, which may lead to better treatment results.[164] Its potential as a complete therapeutic agent is increased by its multitargeted effects on other signaling pathways, such as mTOR and NF-κB. The PI3K/AKT pathway in breast cancer is disrupted by the primary catechin in green tea, EGCG. Reduced cell proliferation and higher apoptosis are the results of downregulating AKT activity.[165] The antioxidant characteristics of EGCG let it target cancer cells in a targeted manner. Furthermore, EGCG's anti-angiogenic properties may prevent tumor vascularization, reducing the likelihood of metastatic spread. The flavonoid quercetin, which may be found in a variety of plant sources, inhibits the PI3K/AKT pathway. Cell cycle arrest and death in breast cancer cells are the results of it impairing PI3K activity and downregulating AKT signaling.[166]The possible anti-inflammatory characteristics of quercetin may also contribute to its tumor-suppressing qualities, making it a promising subject for future study. Breast cancer's PI3K/AKT pathway is affected by genistein, which is rich in soy products. It can restore PTEN expression, block PI3K activation, and lower AKT signaling, which decreases cell growth and increases apoptosis.[167] The estrogen-like characteristics of genistein may be advantageous in breast tumors that express hormone receptors, thus providing a dual mechanism of action. Intriguing possibilities may arise from combining these natural substances with traditional treatments or other natural agents.[168] For instance, combining curcumin with chemotherapeutic medications may increase therapy effectiveness and minimize side effects. These drugs' synergistic effects on the PI3K/AKT pathway and their diverse target effects show the possibility of combination approaches for the best therapeutic results.[169]

4.3 Preclinical and clinical evidence of pathway inhibition

A potential approach in the treatment of breast cancer is the suppression of signaling pathways, such as the PI3K/AKT pathway.[170] Insights into the efficacy of pathway inhibition have been gained from both preclinical researches done in laboratory settings and clinical trials involving

actual patients.[171] Table 1 provides an overview of the data supporting pathway inhibition in the management of breast cancer.

Table 1: Evidence of pathway blockage in breast cancer from preclinical and clinical studies

Evidence	Preclinical Studies	Clinical Studies	References
Cell line studies	Natural substances like resveratrol and curcumin block the PI3K/AKT pathway in breast cancer cell lines. - Cell growth was reduced, while apoptosis was raised. - Preventing invasion and migration	Pathway inhibitors' safety and dosage are being evaluated in phase I studies. Natural agents that target PI3K/AKT have little clinical support	[172,173]
Xenograft models	In animal models, drugs that target the PI3K/AKT pathway demonstrate decreased tumor development. - Suppressed angiogenesis was found improved sensitivity to chemotherapy	The efficacy of pathway inhibitors in patients with breast cancer is being studied in phase II studies. - Modulation of biomarkers that suggest pathway modification	[174]
Mechanistic insights	Studies have shown that natural chemicals may modify important molecules in pathways. Cell cycle arrest, altered gene expression, and the triggering of apoptosis in breast cancer cells	Combination therapy using route blockers and traditional medicines has been investigated. - improved treatment	[175]

5 MAPK Pathway Targeting

Cell proliferation, differentiation, migration, and survival are just a few of the many cellular activities that are regulated by the MAPK pathway, a crucial signaling cascade. The development and spread of breast cancer are often linked to the dysregulation of this system. The MAPK pathway has been identified as a possible target for therapeutic intervention in the etiology of breast cancer, and natural chemicals provide exciting therapeutic options. Numerous growth factors and receptors that inhibit receptor tyrosine kinases stimulate the MAPK pathway.[176] These RTKs, like the human epidermal growth factor receptor 2 (HER2) or the EGFR, may be inhibited by natural substances, which can stop the MAPK pathway from working further down the line. These receptors have been demonstrated to be modulated by substances like curcumin and resveratrol, which inhibits the signaling of these receptors in breast cancer cells. Natural substances may block important kinases in the MAPK pathway via

kinase inhibition. For example, substances like curcumin and EGCG have been discovered to inhibit the activity of MAPK kinases (MEKs), which are significant intermediates in the process.[177,178] This inhibitor slows the development of cancer cells by interfering with downstream signaling. Natural substances may influence a number of the MAPK pathway's downstream elements, including the ERK proteins.[179] The expression of genes important in cell proliferation, survival, and metastasis is decreased by these substances' interference with ERK activation. Breast cancer cells may be made to undergo apoptosis by substances that target the MAPK pathway.[180] Cancer cells may die as a result of their ability to upregulate pro-apoptotic proteins and downregulate anti-apoptotic elements. Strategies in Combination the PI3K/AKT pathway and the MAPK pathway are both often addressed in conjunction with traditional therapy. By making cancer cells more susceptible to treatment, natural substances may improve the effectiveness of chemotherapy or targeted treatments. Therapies may become resistant if it is difficult to block the MAPK pathway. Natural substances that affect this system may be able to circumvent resistance mechanisms, rendering cancer cells more amenable to therapy.[181] Some natural substances have an effect on gene expression via the MAPK pathway, according to nutrigenomic techniques. Understanding how dietary elements interact with genes is a key component of nutrigenomic techniques, which serve as the basis for customized therapies. Effects that rely on context: It's vital to keep in mind that targeting the MAPK pathway may have context-dependent effects. Inhibiting the MAPK pathway may have different outcomes depending on the cancer's genetic makeup and the particular mutations that are present.[182]

5.1 Exploration of natural compounds impacting the MAPK pathway

The Mitogen-Activated Protein Kinase (MAPK) pathway is a crucial signaling cascade that controls important cellular processes linked to the initiation and progression of breast cancer see Figure 3.

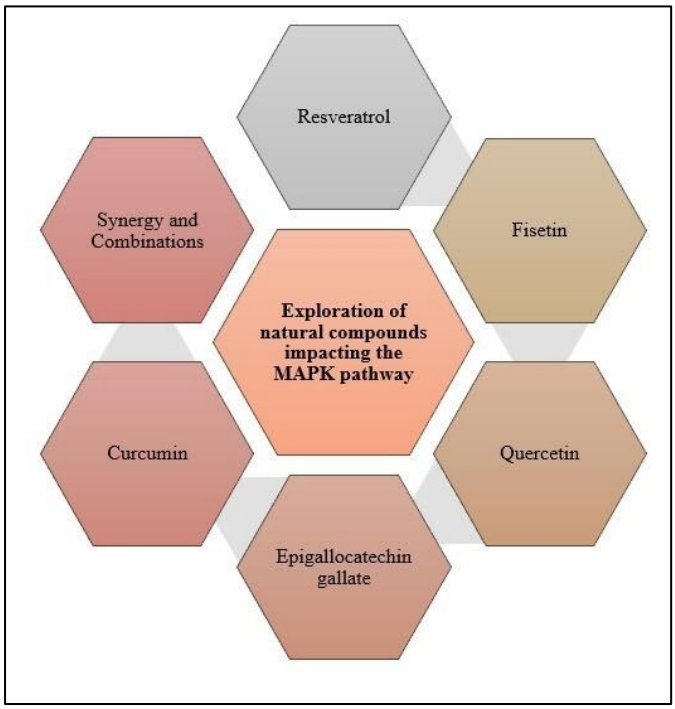

Figure 3. Targeting this route with natural chemicals generated from diverse sources has shown potential

It has been investigated how turmeric's bioactive component curcumin affects the MAPK pathway.[183] It may prevent MEK and ERK from being activated, hence reducing cancer cell invasion, proliferation, and angiogenesis. Because of curcumin's capacity to target the MAPK pathway as well as its anti-inflammatory effects, it may be useful as a breast cancer treatment. Resveratrol, which is present in berries and grapes, has been shown to have an impact on the MAPK pathway. It prevents ERK from being phosphorylated, which inhibits cell proliferation, migration, and the induction of apoptosis in breast cancer cells.[184] Its promise as a natural agent for breast cancer intervention is increased by the compound's multitargeted properties, which include antioxidant and anti-inflammatory activity.[185] A significant catechin found in green tea called EGCG (Epigallocatechin Gallate) has shown potential in blocking the MAPK pathway. It may inhibit the phosphorylation of ERK, which reduces cancer cell proliferation, and invasion, and increases apoptosis sensitivity. The antioxidant qualities of EGCG increase its potential as an additional treatment for breast cancer.[186] Quercetin is a flavonoid that may be found in a variety of plant sources, and its impact on the MAPK pathway has been studied. It may prevent the activation of MEK/ERK, which inhibits breast cancer cell growth, migration, and angiogenesis.[187] The putative anti-inflammatory effects of quercetin also influence the pathway. Fisetin has been investigated for its ability to modulate the MAPK pathway and is found in fruits like strawberries. It can downregulate phosphorylated ERK, which reduces cell invasion and migration.[188] Fisetin has a greater promise as a natural molecule for treating breast cancer because of its capacity to affect several signaling pathways. Studies of synergy and combinations of organic substances that target the MAPK pathway together with conventional medicines are common. [189] They may have synergistic effects on breast cancer treatment due to their capacity to boost the effects of natural agents or chemotherapy-targeted treatments.[190] Although preclinical data is encouraging in terms of clinical translation, clinical studies are required to confirm the effectiveness and safety of these natural substances in breast cancer patients. Insights regarding their potential as additional or stand-alone therapy will emerge from phase II studies evaluating their effect on the MAPK pathway and clinical outcomes.[191]

5.2 Analysis of compound's effects on cell proliferation and survival

Natural substances including curcumin, resveratrol, EGCG, quercetin, and fisetin have shown unique impacts on breast cancer cell growth and survival. Reduced proliferation and increased apoptosis are the results of curcumin and resveratrol's inhibition of the MAPK and MEK/ERK pathways, respectively.[192] EGCG inhibits phosphorylated ERK, which reduces proliferation and boosts apoptosis. Quercetin prevents MEK/ERK activation, reduces proliferation, and induces apoptosis. Fisetin targets phosphorylated ERK, inhibits proliferation, and encourages death.[193] These substances have a variety of effects, altering signaling pathways that affect the survival and proliferation of breast cancer cells see Table 2.

Table 2: Investigation of the impact of natural substances on breast cancer cell survival and proliferation

Natural compound	**Mechanism of action**	**Effect on cell proliferation**	**Effect on cell survival**	**References**
Curcumin	Inhibits MAPK pathway, induces apoptosis	Decreased proliferation	Induces apoptosis	[194]
Resveratrol	Suppresses MEK/ERK activation and promotes apoptosis	Inhibits proliferation	Enhances apoptosis	[195]
EGCG (Green Tea)	Downregulates phosphorylated ERK, promotes apoptosis	Reduces proliferation	Induces apoptosis	[196]
Quercetin	Inhibits MEK/ERK activation, modulates cell cycle	Suppresses proliferation	Promotes apoptosis	[197]
Fisetin	Downregulates phosphorylated ERK, modulates cell cycle	Decreases proliferation	Induces apoptosis	[198]

6 Wnt/β-catenin Pathway Targeting

Embryonic development, tissue homeostasis, and stem cell control are among the biological activities in that the Wnt/β-catenin pathway is crucial. [199] [The] development, spread, and metastasis of breast cancer are linked to the dysregulation of this system. A potentially effective strategy for treating breast cancer is to target the Wnt/β-catenin pathway, and natural substances provide possible interventional tactics.[200] Natural chemicals that target Wnt ligands may sabotage the Wnt signaling cascade. For instance, certain substances bind to the Wnt proteins, preventing them from interacting with cell surface receptors. As a result, the Wnt/-catenin pathway cannot start, and its cancer-causing effects are reduced. Natural substances can control the amount of -catenin, a key participant in the process, by modulating its concentration.[201] They could encourage cytoplasmic β-catenin's breakdown, which would prevent it from moving into the nucleus and inhibiting transcription.[202] The Wnt target genes involved in cell survival and proliferation have their expression attenuated by this. Wnt signals must be transmitted with the interference of disordered proteins. Dvl may be inhibited by natural substances, preventing the Wnt/-β catenin pathway's ability to transmit signals. Oncogenic gene expression pathways can't get started because of this interruption. In addition to PI3K/AKT and MAPK pathways, the Wnt/β-catenin pathway also interacts with additional

signaling cascades. Breast cancer cell growth and survival may be further hampered by natural substances that target both pathways due to their synergistic effects. The expression of some natural substances that affect epigenetic changes, such as the Wnt/β-catenin pathway, may be changed. These drugs may reestablish a healthy balance between tumor-suppressive and oncogenic Wnt signaling by altering DNA methylation and histone changes.[203] The Wnt/β-catenin pathway may be affected more significantly by natural chemicals when they are combined with conventional treatments. It may be more effective to combine these substances with chemotherapy or other targeted treatments to improve therapeutic results and prevent the establishment of resistance.[204] Despite encouraging preclinical results, issues with bioavailability and specificity must be resolved for clinical translation. The multitargeted actions of natural substances could be advantageous for avoiding compensatory mechanisms and lowering toxicity.[205]

6.1 In-depth review of natural compounds modulating the Wnt/β-catenin pathway

The Wnt/β-catenin pathway is a significant signaling cascade involved in stem cell control, tissue homeostasis, and embryonic development. This pathway's dysregulation has been linked to the development, spread, and metastasis of breast cancer.[206] The Wnt/β-catenin pathway has been modulated by natural substances taken from a variety of sources, potentially opening up new therapeutic approaches. Here, we examine in-depth the impact of a few natural substances on the Wnt/β-catenin pathway in breast cancer.[207] Due to its ability to block the Wnt/β-catenin pathway, the polyphenol curcumin, which is present in turmeric, has attracted interest. It targets a variety of substances, such as Wnt ligands, receptors, and β-catenin. Inhibiting cell growth and promoting death in breast cancer cells, curcumin downregulates the expression of Wnt target genes.[208] Its promise as a treatment tool is aided by its capacity to modify the route at numerous stages. Sulforaphane, which is common in cruciferous vegetables, has been shown to block the Wnt/β-catenin pathway by lowering levels of β-catenin.[209] The nuclear translocation and subsequent gene transcription of -catenin are prevented because it triggers the proteasomal destruction of the protein. Breast cancer cells' proliferation and invasion are reduced as a result of sulforaphane's actions.[210] The Wnt/β-catenin pathway is inhibited by the flavonoids epigallocatechin gallate from green tea and quercetin from diverse plant sources.[211] By preventing Wnt ligand-receptor interactions and β-catenin nuclear translocation, EGCG blocks the pathway. Breast cancer cell growth and death are impacted by quercetin's inhibition of -catenin signaling and downstream gene expression. It has been investigated how genistein, which is included in soy products, affects the Wnt/β-catenin pathway. It interferes with -catenin's interaction with the transcription factors T-cell factor (TCF) and lymphoid enhancer factor (LEF) as well as the nuclear accumulation of -catenin. [212] The effects of genistein inhibit breast cancer cell invasion and proliferation[213]. In grapes and berries, resveratrol inhibits the expression of Wnt target genes and decreases -catenin levels, which affects the Wnt/β-catenin pathway.[214] This inhibition helps to increase apoptosis while reducing the proliferation and migration of breast cancer cells. Although preclinical investigations on these natural chemicals have shown promise, issues with bioavailability and selectivity continue to stand in the way of clinical use.[215] To effectively target the Wnt/β-catenin pathway in breast cancer patients, further research is required to improve formulations, doses, and delivery strategies.[216]

6.2 Examination of compounds' impact on cancer stemness and metastasis

Critical factors that affect breast cancer growth, therapeutic resistance, and patient outcomes include cancer stemness and metastasis. Due to their ability to affect these complex processes, natural chemicals produced from numerous sources have attracted a lot of attention.[217] Here, we examine a few natural substances and their effects on breast cancer metastasis and cancer stemness. Turmeric's polyphenolic component curcumin has a variety of effects on the development and spread of cancer. By stifling self-renewal pathways and fostering differentiation, it targets cancer stem cells (CSCs).[218,219] Additionally, curcumin prevents the epithelial-mesenchymal transition (EMT), hence reducing the possibility of metastatic spread. Its promise as a treatment tool is aided by its capacity to alter several signaling cascades.[220] Sulforaphane, which is prevalent in cruciferous vegetables, has shown potential for reducing cancer stemness. It causes apoptosis and inhibits CSC growth.[221] Through its reduction of EMT-related factors and prevention of cancer cell invasion and migration, sulforaphane has a negative influence on metastasis.[222] Green tea's epigallocatechin gallate (EGCG) has a variety of impacts on the stemness and metastasis of cancer. Encouraging divergence hinders CSC self-renewal.[223] The development of invasive traits is inhibited by EGCG's inhibition of EMT-related genes. By reducing cell migration and inhibiting matrix metalloproteinases, it minimizes the likelihood of metastatic spread. Resveratrol, which may be found in berries and grapes, has a variety of impacts on the growth and spread of cancer. It inhibits CSC self-renewal and encourages differentiation, which reduces the likelihood that they may initiate tumors.[224] By preventing invasion and migration, resveratrol's regulation of EMT markers and encouragement of mesenchymal-epithelial transition prevent metastasis. By inhibiting self-renewal pathways and promoting differentiation, the flavonoid quercetin, which is found in many plant sources, regulates cancer stemness. It affects metastasis by blocking EMT-related processes and limiting cell invasion and migration. Despite encouraging preclinical results, clinical translation of these natural medicines faces obstacles including bioavailability and targeted delivery.[225] To confirm their impact on cancer stemness and metastasis in breast cancer patients, rigorous clinical studies are required. These chemicals have the potential to be complementing elements of cutting-edge breast cancer therapy regimens because of the many ways through which they affect these processes.[226]

6.3 Potential for disrupting oncogenic signaling

The development and spread of breast cancer are heavily influenced by oncogenic signaling pathways. It has become clear that blocking these routes may slow the spread of cancer and enhance therapy results. [227] Natural substances originating from a variety of sources provide a potential arsenal of agents that might interfere with oncogenic signaling, offering cutting-edge methods for breast cancer treatments. Oncogenic signaling pathways are often affected in several ways by natural substances.[228] Cross-talk and compensatory mechanisms that support cancer cell survival and proliferation may be prevented by their capacity to control different elements within a pathway or target several pathways concurrently. Natural substances can directly target important molecules inside neoplastic pathways, preventing their activation.[229] For instance, substances like curcumin, resveratrol, and EGCG have shown the capacity to inhibit a variety of signaling molecules, such as kinases or transcription factors, resulting in the

blockage of a pathway. Multiple signaling pathways are affected by a variety of natural substances, which cause apoptosis in cancer cells. These chemicals efficiently reduce the survival advantage provided by oncogenic signaling by causing cell death and blocking survival pathways.[230] Resistance to therapy may be influenced by oncogenic pathways. By disrupting the pathways that support survival despite treatments, natural substances have shown promise in overcoming resistance mechanisms. This makes them excellent resources for boosting the effectiveness of already used medicines.[231] Oncogenic signaling-related gene expression patterns are influenced by the epigenetic impacts of several natural substances. These substances may disrupt carcinogenic pathways by altering DNA methylation and histone alterations, which can restore the equilibrium between tumor suppressors and oncogenes.[232] Metastasis, a significant obstacle in the treatment of breast cancer, may be prevented by natural substances that interfere with oncogenic signaling. These substances slow down the spread of cancer cells to distant areas by altering pathways involved in migration, invasion, and angiogenesis.[233] Different oncogenic signaling patterns originate from the specific genetic composition of each patient's cancer. Natural substances may be specifically formulated to target unique oncogenic pathways because of their different mechanisms of action. This makes them good candidates for personalized therapy regimens.[234]

7 Combination Therapies and Synergy

Modern oncology is characterized by the fusion of many therapeutic techniques to produce synergistic results. Combination therapy for breast cancer has shown significant promise for improving treatment results, overcoming resistance, and minimizing adverse effects. A potential way to achieve synergy and improve therapeutic approaches is to combine natural chemicals with conventional therapies. [235] Chemotherapy's cytotoxic effects on cancer cells may be improved by adding natural substances to it. For instance, substances like curcumin or resveratrol make cancer cells more sensitive to chemotherapy, which makes them more susceptible to cell death. This dual strategy lessens the side effects of chemotherapy while increasing therapeutic response. The benefits of targeted treatments, such as hormone therapy or drugs that target the HER2 gene, may be enhanced by natural substances. When these therapies are combined with organic substances that target signaling pathways, the blockage of oncogenic signals is amplified, perhaps delaying the emergence of resistance. The difficulty of resistance to chemotherapy or targeted treatments still exists.[236] By focusing on different routes or mechanisms of resistance, natural substances may aid in overcoming this resistance. This complementary strategy re-sensitizes cancer cells resistant to traditional therapies. The development and metastasis of tumors may be prevented by combining anti-angiogenic therapy with organic substances. Angiogenesis inhibitors and natural substances like resveratrol or EGCG may work together to further reduce the tumor's blood supply and slow its growth. Immune-modulating properties of natural substances may work in conjunction with immunotherapies. These substances improve the effectiveness of immunotherapeutic methods by boosting the immune response against cancer cells and making the environment favorable for tumor development.[237] The features of each patient's cancer are distinct, requiring individualized treatment plans. Depending on a person's oncogenic signaling profile, different natural substances may be used to maximize synergistic effects unique to their cancer subtype. Clinical trials are built on the results of preclinical investigations demonstrating the interaction

between natural substances and established treatments. To confirm the security, effectiveness, and possible advantages of combination therapy in breast cancer patients, phase I and phase II studies are essential.[238]

7.1 Discussion of combining natural compounds with standard treatments

A potential strategy to improve therapy results and address the difficulties presented by cancer development, resistance, and side effects is the combination of natural substances with conventional medicines in the management of breast cancer. These combinations have the potential to completely alter the therapeutic landscape and enhance patient outcomes due to their synergistic effects.[239] Here, we look into the salient features of mixing natural substances with conventional therapies for breast cancer. It is possible to increase the effectiveness of treatment by combining natural substances with common medications like chemotherapy or targeted therapies.[240] Natural substances may promote tumor regression and disease management by making cancer cells more susceptible to the cytotoxic effects of standard treatments. This is accomplished via a variety of modes of action. One of the biggest challenges in managing breast cancer is resistance to conventional therapies. Natural substances have shown promise in reversing or defeating resistance processes. These substances resensitize resistant cancer cells, possibly restoring therapy efficacy, by focusing on alternate routes or encouraging apoptosis. The quality of life for patients is often adversely affected by common therapies.[241] These negative effects may be reduced by incorporating natural substances. Compounds like curcumin or EGCG have shown anti-inflammatory and antioxidant capabilities, which help offset toxicities brought on by therapy. The underlying oncogenic pathways of a patient's cancer may help guide the selection of natural substances. It is possible to completely block a variety of oncogenic signals by combining drugs that target certain signaling pathways with conventional therapy, which lowers the risk of developing resistance. [242] The features of each patient's cancer vary. Personalized treatment plans are possible with the use of natural ingredients. Combining drugs that are customized to a person's oncogenic profile increases the likelihood of producing synergistic effects that are particular to their cancer subtype.[243] The potential advantages are encouraging, but there are still obstacles to overcome, such as problems with chemical bioavailability, the best dosage, and possible interactions with conventional therapies. To confirm the safety, effectiveness, and possible advantages of these combinations, thorough preclinical research and thoughtful clinical trials are required. Oncologists, researchers, and patients must work together to include natural substances with conventional therapies. To achieve the best therapeutic synergy, natural substances will be chosen and dosed based on thorough analyses of patient features and molecular profiles.[244]

7.2 Synergistic effects and enhanced therapeutic outcomes

Investigating the synergistic effects produced by combining several therapy methods has become necessary in the development of better treatment regimens for breast cancer. The incorporation of natural substances with conventional therapies is one approach that has a lot of promise since it aims to take advantage of their various mechanisms of action and improve therapeutic results. By tackling problems like treatment resistance, low effectiveness, and side effects, this synergistic strategy has the potential to completely change how breast cancer is

managed.[245]Natural substances like curcumin, resveratrol, EGCG, and others work synergistically with conventional therapies in a way that outperforms the advantages of each one alone. These substances naturally fight cancer by reducing inflammation, boosting antioxidant levels, and altering certain pathways. They may sensitize cancer cells, rendering them more vulnerable to treatment-induced cell death, when used in conjunction with chemotherapy, targeted treatments, or radiation.[246] Additionally, natural substances can target many signaling pathways concurrently, lowering the risk of resistance formation and increasing the overall efficacy of treatment protocols. Additionally, synergistic benefits include a decrease in treatment-related toxicity.[247] Natural substances' protective qualities may lessen the negative effects of conventional medicines, enhancing the quality of life for patients while they are receiving therapy. In addition to improving medication tolerability, this combined strategy also makes it possible for patients to follow their regimens more successfully. The idea of using natural substances in addition to conventional therapies is intriguing, but careful investigation is necessary before it can be successfully implemented in clinical settings.[248] A well-designed clinical study is required to confirm these benefits in patients with breast cancer since positive preclinical research shows synergy. In addition to assessing effectiveness, these studies will also look at safety, ideal dosage, and any interactions. The search for synergistic effects via the combination of natural chemicals with established therapies has the potential to considerably improve therapeutic results in breast cancer, in conclusion. This cutting-edge method tackles treatment issues from several sides, increasing response rates, overcoming resistance, and reducing treatment-related toxicity. The realization of improved breast cancer treatment outcomes becomes an achievable objective as research and clinical trials go forward, giving patients hope and changing the face of breast cancer care.[249]

7.3 Strategies to overcome resistance and improve treatment efficacy

Treatment resistance is still a major obstacle to managing breast cancer, often reducing the efficacy of medicines and accelerating the course of the illness. Innovative approaches that may circumvent resistance mechanisms and increase treatment effectiveness are necessary to address this problem. Here, we examine several methods for overcoming resistance and improving the treatment results for breast cancer patients.[250] Utilizing a variety of therapeutic approaches, including chemotherapy, targeted treatments, and immunotherapies, may target cancer cells in various ways. This method may concurrently block many routes and prevent the establishment of resistance, increasing the effectiveness of the therapy. Resistance often develops as a result of cancer cells switching their reliance on alternate signaling pathways. Treatment resistance may be overcome and therapeutic responses can be restored by using natural substances or small-molecule inhibitors to target these alternative pathways.[251] The most likely-to-work targeted medicines may be chosen by using molecular profiling to identify certain mutations or variations in each patient's tumor. By limiting needless exposure to unsuccessful therapies, personalized treatment plans may increase treatment effectiveness. Immunotherapies, including immune checkpoint inhibitors, take use of the immune system to attack cancer cells. These medications may break through resistance by triggering immune responses against cancer cells, including those that have become resistant to traditional therapy. By avoiding apoptosis, or programmed cell death, cancer cells often gain resistance.[252] The susceptibility of cancer cells to treatment-induced cell death may be restored by using

techniques to restart apoptotic pathways, such as utilizing BH3 mimics or organic chemicals. Resistance to therapy is influenced by epigenetic changes. [253] Targeting epigenetic alterations with medications or organic substances may undo these modifications, re-sensitizing cancer cells to therapy and enhancing treatment effectiveness. During treatment, regular monitoring of the tumor response and molecular alterations might direct the use of adaptive therapy. These methods enable real-time modifications to therapy regimens, optimizing therapeutic approaches when resistance mechanisms arise.[254]

8 Future Prospects

Clinical trials were crucial in establishing the effectiveness and safety of novel therapies, which have been made possible by advancements in breast cancer research. Clinical studies are now underway and future developments show great potential for improving outcomes for breast cancer patients as the field continues to develop. Clinical studies are evaluating the effectiveness of targeted medicines, such as CDK4/6 inhibitors and HER2-targeted medications, which selectively disrupt the pathways promoting the development of cancer. Through the customization of medicines to unique patient features, these studies seek to improve treatment strategies and minimize negative effects. Clinical studies for breast cancer are looking at immune checkpoint inhibitors and adoptive T-cell therapy. These immunotherapies attempt to take use of the immune system's capacity to identify and target cancer cells, perhaps providing long-lasting effects in certain patient groups. Clinical research focuses on the combination of several therapeutic modalities, including chemotherapy, targeted treatments, and immunotherapies. Through simultaneous attacks on numerous targets, these combination techniques aim to increase therapeutic effectiveness and reduce resistance. Biomarker-Based Strategies To find individuals most likely to benefit from certain therapies, clinical trials are increasingly combining biomarker analysis. This tailored medicine strategy increases the effectiveness of therapy while reducing needless exposure to unsuccessful medicines. Neoadjuvant treatments, which decrease tumors before surgery, are being studied in clinical research, as well as adjuvant therapies, which aim to prevent recurrence. By focusing on residual illness and lowering the chance of recurrence, these methods seek to improve outcomes. Early cancer detection clinical studies are investigating the use of liquid biopsies for early cancer identification and tracking therapeutic response. These non-invasive techniques might change diagnosis and monitoring, enabling earlier intervention and better results. concentrated on the patient Focusing on patient-centered care, which includes shared decision-making, survivorship support, and quality-of-life concerns, is a key component in the treatment of breast cancer in the future. Interventions to control side effects of therapy are also being studied in clinical trials. Innovative trial designs and cutting-edge therapeutic modalities will be driven in the future by cooperation among researchers, doctors, and patients. Individualized therapy will be guided by precision medicine, informed by thorough molecular profiling. Furthermore, improvements in big data analytics and artificial intelligence will make it possible to design clinical trials more efficiently and forecast treatments with greater accuracy. The way for the next study and treatment development has been illuminated by remarkable triumphs, nevertheless. Natural chemicals may have a low bioavailability and complicated pharmacokinetics, making it difficult to administer medications to patients in a way that is both consistent and effective. Specificity Targeting the desired signaling pathways or processes in

people might be difficult since natural substances can have unintended effects. variations in patients Treatments must be tailored to each patient's specific genetic profile due to the variety of breast cancer subtypes and their varying patient responses. Natural substances may interact with conventional therapy, affecting the efficacy of the treatment or producing negative consequences. Regulatory acquiescence to get regulatory clearance for novel treatments, thorough clinical studies are needed, which takes time and money. Protection and acceptability In clinical studies, numerous natural substances demonstrated acceptable safety profiles, which encourages continued research into them as supplements to conventional medicines. Synergistic outcomes Successful clinical trials have shown that the addition of natural substances to conventional therapies may increase their effectiveness while reducing their negative effects. Treatment that is unique the development of tailored therapeutics has been facilitated by biomarker-guided research that has revealed patient subgroups that react well to certain natural substances. Clinical studies that have improved outcomes have shown encouraging trends in terms of slowed tumor development, increased treatment response, and better quality of life for breast cancer patients.[255-305]

9 Conclusion

Natural substances have been investigated as therapeutic agents for breast cancer, and the results have been astounding discoveries and prospective treatment plans. This voyage has shown the complex mechanisms of resistance mechanisms, carcinogenic signaling pathways, and the potential for natural substances to interfere with these systems. It becomes clear that natural substances provide a diverse strategy for treating breast cancer on an individual basis as we review important discoveries and ideas. Research has shown that natural substances like curcumin, resveratrol, EGCG, and others have the power to alter important signaling pathways, suppress cancer growth, stop metastasis, and improve the outcomes of conventional therapies. From early oncogenic signaling to late stages of metastatic dissemination, their multi-targeted activities allow disruption at different degrees of cancer development. These substances have astounding promise for overcoming treatment resistance, increasing therapy effectiveness, and minimizing adverse effects. Because every case of breast cancer is unique, specific treatment strategies are necessary. Natural substances are excellent options for modifying therapy to each patient's specific molecular profile due to their wide range of action mechanisms. By combining these drugs with traditional medicines, it is possible to design individualized regimens that target the unique cancer-causing pathways in each patient, increasing the chance of a successful outcome and reducing the need for ineffective medications. Natural compound-based therapy research is a continuous project that calls for cross-disciplinary cooperation and consistent research efforts. Validation of the safety, effectiveness, and potential advantages of mixing natural substances with conventional therapies requires thorough preclinical research and thoughtful clinical trials. To enable the smooth transition of research results into clinical applications, collaborations between researchers, oncologists, pharmacologists, and patients are essential. Integrating novel strategies will shape the future of breast cancer therapy, and medicines based on natural compounds will be essential. Predictive modeling may help with treatment choices, improving the accuracy of therapy selection as artificial intelligence and big data analytics progress. Furthermore, a potential frontier that ought to drive the development of treatment techniques is patient-centered care that incorporates patients' desires and well-

being. The investigation of natural compound-based medicines for the treatment of breast cancer has, in conclusion, shown a promising and innovative route. These drugs provide a multifaceted strategy for attacking cancer's weaknesses, overcoming resistance, and improving therapy results.

Acknowledgments

The authors are thankful to the Principal, Department of Pharmacy, Teerthanker Mahaveer University, Moradabad for providing the necessary facilities.

Competing interest statement

The authors declare no conflict of interest.

Disclaimer

None

List of abbreviations

MAPK	Mitogen-activated protein kinases
MMPs	Matrix metalloproteinases
DNA	Deoxyribonucleic acid
PI3K	Phosphatidylinositol 3-kinase
ERK	Extracellular signal-regulated kinase
EMT	Epithelial-mesenchymal transition
VEGF	Vascular endothelial growth factor
PR	Progesterone receptors
ER	Estrogen receptors
AR	Androgen receptors
RTKs	Receptor tyrosine kinases
EGFR	Epidermal growth factor receptor
CDK	Cyclin-dependent kinases
EGG	Epigallocatechin gallate
MAPK	Mitogen-activated protein kinase
LEF	Lymphoid enhancer factor

References

1. De Souza, Jonas A., Bijou Hunt, Fredrick Chite Asirwa, Clement Adebamowo, and Gilberto Lopes. "Global health equity: cancer care outcome disparities in high-, middle-, and low-income countries." *Journal of Clinical Oncology* 34, no. 1 (2016): 6.

2. Hasanpourghadi, Mohadeseh, Ashok Kumar Pandurangan, and Mohd Rais Mustafa. "Modulation of oncogenic transcription factors by bioactive natural products in breast cancer." *Pharmacological research* 128 (2018): 376-388.

3. Roy, Ankan, and Samir Kumar Patra. "Lipid raft facilitated receptor organization and signaling: a functional rheostat in embryonic development, stem cell biology and cancer." *Stem Cell Reviews and Reports* 19, no. 1 (2023): 2-25.

4. Pathania, Divya, Melissa Millard, and Nouri Neamati. "Opportunities in discovery and delivery of anticancer drugs targeting mitochondria and cancer cell metabolism." *Advanced drug delivery reviews* 61, no. 14 (2009): 1250-1275.

5. Jain, Chitra, Shivani Khatana, and Rekha Vijayvergia. "Bioactivity of secondary metabolites of various plants: a review." *Int. J. Pharm. Sci. Res* 10, no. 2 (2019): 494-504.

6. Joyce, Kieran, Georgina Targa Fabra, Yagmur Bozkurt, and Abhay Pandit. "Bioactive potential of natural biomaterials: Identification, retention and assessment of biological properties." *Signal Transduction and Targeted Therapy* 6, no. 1 (2021): 122.

7. Fouassier, L., Marzioni, M., Afonso, M. B., Dooley, S., Gaston, K., Giannelli, G., ... & Coulouarn, C. (2019). Signalling networks in cholangiocarcinoma: Molecular pathogenesis, targeted therapies and drug resistance. *Liver International*, *39*, 43-62.

8. Crudden, C., Song, D., Cismas, S., Trocmé, E., Pasca, S., Calin, G. A., ... & Girnita, L. (2019). Below the surface: IGF-1R therapeutic targeting and its endocytic journey. *Cells*, *8*(10), 1223.

9. Abdul Manap, A. S., Wei Tan, A. C., Leong, W. H., Yin Chia, A. Y., Vijayabalan, S., Arya, A., ... & Madhavan, P. (2019). Synergistic effects of curcumin and piperine as potent acetylcholine and amyloidogenic inhibitors with significant neuroprotective activity in SH-SY5Y cells via computational molecular modeling and in vitro assay. *Frontiers in aging neuroscience*, *11*, 206.

10. Zhou, R., Chen, H., Chen, J., Chen, X., Wen, Y., & Xu, L. (2018). Extract from Astragalus membranaceus inhibit breast cancer cells proliferation via PI3K/AKT/mTOR signaling pathway. *BMC Complementary and Alternative Medicine*, *18*, 1-8.

11. Holman, C., & Villers-Sidani, E. D. (2014). Indestructible plastic: the neuroscience of the new aging brain. *Frontiers in Human Neuroscience*, *8*, 219.

12. Ogunkorode, R. S. A., Holtslander, L., Ferguson, L., Maree, J. E., Anonson, J., & Ramsden, V. R. (2021). Factors influencing the health-seeking behaviors of women with advanced stages of breast cancer in Southwestern Nigeria: An interpretive description study. *International Journal of Africa Nursing Sciences*, *14*, 100273.

13. Conneely, O. M., Jericevic, B. M., & Lydon, J. P. (2003). Progesterone receptors in mammary gland development and tumorigenesis. *Journal of mammary gland biology and neoplasia*, *8*, 205-214.

14. Beňačka, R., Szabóová, D., Guľašová, Z., Hertelyová, Z., & Radoňák, J. (2022). Classic and new markers in diagnostics and classification of breast cancer. *Cancers*, *14*(21), 5444.

15. Rakha, E. A., Reis-Filho, J. S., & Ellis, I. O. (2008). Basal-like breast cancer: a critical review. *Journal of clinical oncology*, *26*(15), 2568-2581.

16. Islam, M. R., Islam, F., Nafady, M. H., Akter, M., Mitra, S., Das, R., ... & Cavalu, S. (2022). Natural small molecules in breast cancer treatment: understandings from a therapeutic viewpoint. *Molecules*, *27*(7), 2165.

17. Radley, A., & Bell, S. E. (2007). Artworks, collective experience and claims for social justice: The case of women living with breast cancer. *Sociology of health & illness*, *29*(3), 366-390.

18. Retsky, M., Demicheli, R., Hrushesky, W., Baum, M., & Gukas, I. (2010). Surgery triggers outgrowth of latent distant disease in breast cancer: an inconvenient truth?. *Cancers*, *2*(2), 305-337.

19. Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., ... & Ren, G. (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & diseases*, *5*(2), 77-106.

20. Tao, Z., Shi, A., Lu, C., Song, T., Zhang, Z., & Zhao, J. (2015). Breast cancer: epidemiology and etiology. *Cell biochemistry and biophysics*, *72*, 333-338.

Chicago starts

21. Mettlin, Curtis. "Global breast cancer mortality statistics." *CA: a cancer journal for clinicians* 49, no. 3 (1999): 138-144.

22. Bray, Freddie, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L. Siegel, Lindsey A. Torre, and Ahmedin Jemal. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: a cancer journal for clinicians* 68, no. 6 (2018): 394-424.

23. Jelovac, D., & Armstrong, D. K. (2011). Recent progress in the diagnosis and treatment of ovarian cancer. *CA: a cancer journal for clinicians*, *61*(3), 183-203. APA

24. Kornblith, A. B., Herndon, J. E., Zuckerman, E., Viscoli, C. M., Horwitz, R. I., Cooper, M. R., ... & Cancer and Leukemia Group B. (2001). Social support as a buffer to the psychological impact of stressful life events in women with breast cancer. *Cancer*, *91*(2), 443-454. APA

25. Boykoff, Nelli, Mona Moieni, and Saskia Karen Subramanian. "Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response." *Journal of cancer survivorship* 3 (2009): 223-232.

26. Stenberg, Una, Cornelia M. Ruland, and Christine Miaskowski. "Review of the literature on the effects of caring for a patient with cancer." *Psycho-oncology* 19, no. 10 (2010): 1013-1025.

27. Feng, Yixiao, Mia Spezia, Shifeng Huang, Chengfu Yuan, Zongyue Zeng, Linghuan Zhang, Xiaojuan Ji et al. "Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis." *Genes & diseases* 5, no. 2 (2018): 77-106.

28. Horgan, Denis, Tanja Čufer, Francesco Gatto, Iwona Lugowska, Donatella Verbanac, Ângela Carvalho, Jonathan A. Lal et al. "Accelerating the development and validation of liquid biopsy for early cancer screening and treatment tailoring." In *Healthcare*, vol. 10, no. 9, p. 1714. MDPI, 2022.

29. Demirkan, Haluk. "A smart healthcare systems framework." *It Professional* 15, no. 5 (2013): 38-45.

30. Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., ... & Ren, G. (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & diseases*, *5*(2), 77-106.

31. Matés, José M., Juan A. Segura, Francisco J. Alonso, and Javier Márquez. "Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis." *Archives of toxicology* 82 (2008): 273-299.

32. Kim, Eun Kyung, and Eui-Ju Choi. "Compromised MAPK signaling in human diseases: an update." *Archives of toxicology* 89 (2015): 867-882.

33. Moschetta, M., A. Reale, C. Marasco, A. Vacca, and M. R. Carratù. "Therapeutic targeting of the mTOR-signalling pathway in cancer: benefits and limitations." *British journal of pharmacology* 171, no. 16 (2014): 3801-3813.

34. Lindsey, Stephan, and Sigrid A. Langhans. "Crosstalk of oncogenic signaling pathways during epithelial–mesenchymal transition." *Frontiers in oncology* 4 (2014): 358.

35. Park, Moon-Taek, and Su-Jae Lee. "Cell cycle and cancer." *BMB Reports* 36, no. 1 (2003): 60-65.

36. Ahmed, Jahangir. "Optimisation of the Lister strain of vaccinia virus for use as an anticancer immunotherapeutic agent." PhD diss., Queen Mary University of London, 2015.

37. Pęczek, Piotr, Monika Gajda, Kacper Rutkowski, Marta Fudalej, Andrzej Deptała, and Anna M. Badowska-Kozakiewicz. "Cancer-associated inflammation: pathophysiology and clinical significance." *Journal of cancer research and clinical oncology* 149, no. 6 (2023): 2657-2672.

38. Zitvogel, Laurence, Antoine Tesniere, and Guido Kroemer. "Cancer despite immunosurveillance: immunoselection and immunosubversion." *Nature reviews immunology* 6, no. 10 (2006): 715-727.

39. Kciuk, Mateusz, Damian Kołat, Żaneta Kałuzińska-Kołat, Mateusz Gawrysiak, Rafał Drozda, Ismail Celik, and Renata Kontek. "PD-1/PD-L1 and DNA damage response in cancer." *cells* 12, no. 4 (2023): 530.

40. Shen, Changxian, Yuqi He, Qiang Chen, Haihua Feng, Terence M. Williams, Yuanzhi Lu, and Zhengfu He. "Narrative review of emerging roles for AKT-mTOR signaling in cancer radioimmunotherapy." *Annals of Translational Medicine* 9, no. 20 (2021).

41. Marchesi, Vincent T. "Alzheimer's dementia begins as a disease of small blood vessels, damaged by oxidative-induced inflammation and dysregulated amyloid metabolism: implications for early detection and therapy." *The FASEB Journal* 25, no. 1 (2011): 5-13.

42. Misawa, Aya, and Satoshi Inoue. "Estrogen-related receptors in breast cancer and prostate cancer." *Frontiers in endocrinology* 6 (2015): 83.

43. Daiber, Andreas. "Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species." *Biochimica et Biophysica Acta (BBA)-Bioenergetics* 1797, no. 6-7 (2010): 897-906.

44. Tribondeau, Alicia, Laurent M. Sachs, and Nicolas Buisine. "Tetrabromobisphenol A effects on differentiating mouse embryonic stem cells reveals unexpected impact on immune system." *Frontiers in Genetics* 13 (2022): 996826.

45. Dias, Daniel A., Sylvia Urban, and Ute Roessner. "A historical overview of natural products in drug discovery." *Metabolites* 2, no. 2 (2012): 303-336.

46. Saxena, Mamta, Jyoti Saxena, Rajeev Nema, Dharmendra Singh, and Abhishek Gupta. "Phytochemistry of medicinal plants." *Journal of pharmacognosy and phytochemistry* 1, no. 6 (2013): 168-182.

47. Harvey, Alan L. "Natural products in drug discovery." *Drug discovery today* 13, no. 19-20 (2008): 894-901.

48. Bhullar, Khushwant S., Naiara Orrego Lagarón, Eileen M. McGowan, Indu Parmar, Amitabh Jha, Basil P. Hubbard, and HP Vasantha Rupasinghe. "Kinase-targeted cancer therapies: progress, challenges and future directions." *Molecular cancer* 17 (2018): 1-20.

49. Trindade, Marla, Leonardo Joaquim Van Zyl, José Navarro-Fernández, and Ahmed Abd Elrazak. "Targeted metagenomics as a tool to tap into marine natural product diversity for the discovery and production of drug candidates." *Frontiers in microbiology* 6 (2015): 890.

50. Süntar, Ipek. "Importance of ethnopharmacological studies in drug discovery: role of medicinal plants." *Phytochemistry Reviews* 19, no. 5 (2020): 1199-1209.

51. Holdt, Susan Løvstad, and Stefan Kraan. "Bioactive compounds in seaweed: functional food applications and legislation." *Journal of applied phycology* 23 (2011): 543-597.

52. Nakamura, Kyohei, and Mark J. Smyth. "Targeting cancer-related inflammation in the era of immunotherapy." *Immunology and cell biology* 95, no. 4 (2017): 325-332.

53. Stegmeier, F., M. Warmuth, W. R. Sellers, and M. Dorsch. "Targeted cancer therapies in the twenty-first century: lessons from imatinib." *Clinical Pharmacology & Therapeutics* 87, no. 5 (2010): 543-552.

54. Wells, Andrew S., Gregory L. Finch, Peter C. Michels, and John W. Wong. "Use of Enzymes in the Manufacture of Active Pharmaceutical Ingredients A Science and Safety-Based Approach To Ensure Patient Safety and Drug Quality." *Organic Process Research & Development* 16, no. 12 (2012): 1986-1993.

55. Charman, William N., Hak-Kim Chan, Barrie C. Finnin, and Susan A. Charman. "Drug delivery: A key factor in realising the full therapeutic potential of drugs." *Drug Development Research* 46, no. 3-4 (1999): 316-327.

56. Kim, Jonghoon, Heejun Kim, and Seung Bum Park. "Privileged structures: efficient chemical “navigators” toward unexplored biologically relevant chemical spaces." *Journal of the American Chemical Society* 136, no. 42 (2014): 14629-14638.

57. Sorokina, Maria, and Christoph Steinbeck. "Review on natural products databases: where to find data in 2020." *Journal of cheminformatics* 12, no. 1 (2020): 20.

58. Kopnina, Helen. "Revisiting education for sustainable development (ESD): Examining anthropocentric bias through the transition of environmental education to ESD." *Sustainable development* 22, no. 2 (2014): 73-83.

59. Friedman, Adam A., Anthony Letai, David E. Fisher, and Keith T. Flaherty. "Precision medicine for cancer with next-generation functional diagnostics." *Nature Reviews Cancer* 15, no. 12 (2015): 747-756.

60. Deng, L., Z. Y. Xu-Monette, Sanam Loghavi, G. C. Manyam, Y. Xia, C. Visco, J. Huh et al. "Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era: a report from the International PTL Consortium." *Leukemia* 30, no. 2 (2016): 361-372.

61. Atanasov, Atanas G., Birgit Waltenberger, Eva-Maria Pferschy-Wenzig, Thomas Linder, Christoph Wawrosch, Pavel Uhrin, Veronika Temml et al. "Discovery and resupply of pharmacologically active plant-derived natural products: A review." *Biotechnology advances* 33, no. 8 (2015): 1582-1614.

62. Chhichholiya, Yogita, Prabhat Suman, Sandeep Singh, and Anjana Munshi. "The genomic architecture of metastasis in breast cancer: focus on mechanistic aspects, signalling pathways and therapeutic strategies." *Medical Oncology* 38 (2021): 1-23.

63. Miricescu, Daniela, Alexandra Totan, Iulia-Ioana Stanescu-Spinu, Silviu Constantin Badoiu, Constantin Stefani, and Maria Greabu. "PI3K/AKT/mTOR signaling pathway in breast cancer: from molecular landscape to clinical aspects." *International journal of molecular sciences* 22, no. 1 (2020): 173.

64. Juntilla, Marisa M., and Gary A. Koretzky. "Critical roles of the PI3K/Akt signaling pathway in T cell development." *Immunology letters* 116, no. 2 (2008): 104-110.

65. New, David C., Kelvin Wu, Alice WS Kwok, and Yung H. Wong. "G protein-coupled receptor-induced Akt activity in cellular proliferation and apoptosis." *The FEBS journal* 274, no. 23 (2007): 6025-6036.

66. Li, Qingfang, Zhihui Li, Ting Luo, and Huashan Shi. "Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy." *Molecular Biomedicine* 3, no. 1 (2022): 47.

67. Sanaei, Mohammad-Javad, Sara Razi, Atieh Pourbagheri-Sigaroodi, and Davood Bashash. "The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic

opportunities, challenges, and a glance at the application of nanoparticles." *Translational Oncology* 18 (2022): 101364.

68. Wang, John Q., Eugene E. Fibuch, and Limin Mao. "Regulation of mitogen-activated protein kinases by glutamate receptors." *Journal of neurochemistry* 100, no. 1 (2007): 1-11.

69. Suman, Shankar, Pradeep Kumar Sharma, Girish Rai, Sanjay Mishra, Deepika Arora, Prachi Gupta, and Yogeshwer Shukla. "Current perspectives of molecular pathways involved in chronic inflammation-mediated breast cancer." *Biochemical and biophysical research communications* 472, no. 3 (2016): 401-409.

70. Huang, Xiao Lin, Muhammad Imran Khan, Jing Wang, Rizwan Ali, Syed Wajahat Ali, Ahsan Kazmi, Arbelo Lolai et al. "Role of receptor tyrosine kinases mediated signal transduction pathways in tumor growth and angiogenesis—New insight and futuristic vision." *International Journal of Biological Macromolecules* 180 (2021): 739-752.

71. De Luca, Antonella, Monica R. Maiello, Amelia D'Alessio, Maria Pergameno, and Nicola Normanno. "The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches." *Expert opinion on therapeutic targets* 16, no. sup2 (2012): S17-S27.

72. Yin, Jia-yi, Xin-tong Lu, Meng-ling Hou, Ting Cao, and Zhen Tian. "Sirtuin1-p53: a potential axis for cancer therapy." *Biochemical Pharmacology* (2023): 115543.

73. Flaherty, Keith T., and Grant McArthur. "BRAF, a target in melanoma: implications for solid tumor drug development." *Cancer* 116, no. 21 (2010): 4902-4913.

74. Cassinelli, Giuliana, Valentina Zuco, Laura Gatti, Cinzia Lanzi, Nadia Zaffaroni, Diego Colombo, and Paola Perego. "Targeting the Akt kinase to modulate survival, invasiveness and drug resistance of cancer cells." *Current medicinal chemistry* 20, no. 15 (2013): 1923-1945.

75. Guo, Xiaojia, Lindsay Hollander, Douglas MacPherson, Ling Wang, Heino Velazquez, John Chang, Robert Safirstein, Charles Cha, Fred Gorelick, and Gary V. Desir. "Inhibition of renalase expression and signaling has antitumor activity in pancreatic cancer." *Scientific reports* 6, no. 1 (2016): 22996.

76. Jiang, Wen Guo, Andrew James Sanders, M. Katoh, H. Ungefroren, F. Gieseler, M. Prince, S. K. Thompson et al. "Tissue invasion and metastasis: Molecular, biological and clinical perspectives." In *Seminars in cancer biology*, vol. 35, pp. S244-S275. Academic Press, 2015.

77. Cassinelli, Giuliana, Valentina Zuco, Laura Gatti, Cinzia Lanzi, Nadia Zaffaroni, Diego Colombo, and Paola Perego. "Targeting the Akt kinase to modulate survival, invasiveness and drug resistance of cancer cells." *Current medicinal chemistry* 20, no. 15 (2013): 1923-1945.

78. Lim, Su Yin, Alexander M. Menzies, and Helen Rizos. "Mechanisms and strategies to overcome resistance to molecularly targeted therapy for melanoma." *Cancer* 123, no. S11 (2017): 2118-2129.

79. Houslay, Miles D., and Walter Kolch. "Cell-type specific integration of cross-talk between extracellular signal-regulated kinase and cAMP signaling." *Molecular pharmacology* 58, no. 4 (2000): 659-668.

80. Catassi, A., D. Servent, L. Paleari, A. Cesario, and P. Russo. "Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: implications on lung carcinogenesis." *Mutation Research/Reviews in Mutation Research* 659, no. 3 (2008): 221-231.

81. Stuelten, Christina H., Carole A. Parent, and Denise J. Montell. "Cell motility in cancer invasion and metastasis: insights from simple model organisms." *Nature Reviews Cancer* 18, no. 5 (2018): 296-312.

82. Hirakawa, Satoshi, Lawrence F. Brown, Shohta Kodama, Karri Paavonen, Kari Alitalo, and Michael Detmar. "VEGF-C–induced lymphangiogenesis in sentinel lymph nodes promotes tumor metastasis to distant sites." *Blood* 109, no. 3 (2007): 1010-1017.

83. Fulda, Simone, and Klaus-Michael Debatin. "Resveratrol modulation of signal transduction in apoptosis and cell survival: a mini-review." *Cancer detection and prevention* 30, no. 3 (2006): 217-223.

84. O'Brien, Mauria A., and Rebecca Kirby. "Apoptosis: A review of pro-apoptotic and anti-apoptotic pathways and dysregulation in disease." *Journal of veterinary emergency and critical care* 18, no. 6 (2008): 572-585.

85. Lee, Shannon, Jens Rauch, and Walter Kolch. "Targeting MAPK signaling in cancer: mechanisms of drug resistance and sensitivity." *International journal of molecular sciences* 21, no. 3 (2020): 1102.

86. Zhang, Hengjun, Mozhi Wang, and Yingying Xu. "Understanding the mechanisms underlying obesity in remodeling the breast tumor immune microenvironment: from the perspective of inflammation." *Cancer Biology & Medicine* 20, no. 4 (2023): 268.

87. Tebay, Lauren E., Holly Robertson, Stephen T. Durant, Steven R. Vitale, Trevor M. Penning, Albena T. Dinkova-Kostova, and John D. Hayes. "Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease." *Free Radical Biology and Medicine* 88 (2015): 108-146.

88. Mills, Jamie N., Alex C. Rutkovsky, and Antonio Giordano. "Mechanisms of resistance in estrogen receptor positive breast cancer: overcoming resistance to tamoxifen/aromatase inhibitors." *Current opinion in pharmacology* 41 (2018): 59-65.

89. Kornasio, Reut, Ingo Riederer, Gillian Butler-Browne, Vincent Mouly, Zehava Uni, and Orna Halevy. "β-hydroxy-β-methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1793, no. 5 (2009): 755-763.

90. Jena, Bikash Chandra, and Mahitosh Mandal. "The emerging roles of exosomes in anti-cancer drug resistance and tumor progression: An insight towards tumor-microenvironment

interaction." *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 1875, no. 1 (2021): 188488.

91. Akbarzadeh, Maryam, Ainaz Mihanfar, Shabnam Akbarzadeh, Bahman Yousefi, and Maryam Majidinia. "Crosstalk between miRNA and PI3K/AKT/mTOR signaling pathway in cancer." *Life Sciences* 285 (2021): 119984.

92. Linke, Monika, Stephanie Deborah Fritsch, Nyamdelger Sukhbaatar, Markus Hengstschläger, and Thomas Weichhart. "mTORC 1 and mTORC 2 as regulators of cell metabolism in immunity." *FEBS letters* 591, no. 19 (2017): 3089-3103.

93. Rezatabar, Setareh, Ansar Karimian, Vahid Rameshknia, Hadi Parsian, Maryam Majidinia, Tayebeh Azramezani Kopi, Anupam Bishayee et al. "RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression." *Journal of cellular physiology* 234, no. 9 (2019): 14951-14965.

94. Ashrafizadeh, Milad, Ali Zarrabi, Kiavash Hushmandi, Mahshad Kalantari, Reza Mohammadinejad, Tahereh Javaheri, and Gautam Sethi. "Association of the epithelial–mesenchymal transition (EMT) with cisplatin resistance." *International journal of molecular sciences* 21, no. 11 (2020): 4002.

95. Tang, Dong-Jiang, Sui-Sui Dong, Ning-Fang Ma, Dan Xie, Leilei Chen, Li Fu, Sze Hang Lau, Yan Li, Yan Li, and Xin-Yuan Guan. "Overexpression of eukaryotic initiation factor 5A2 enhances cell motility and promotes tumor metastasis in hepatocellular carcinoma." *Hepatology* 51, no. 4 (2010): 1255-1263.

96. Hu, Zhaoxia, Peipei Wang, Jiaxin Lin, Xingrong Zheng, Fangji Yang, Genglin Zhang, Dabiao Chen et al. "MicroRNA-197 promotes metastasis of hepatocellular carcinoma by activating Wnt/β-catenin signaling." *Cellular Physiology and Biochemistry* 51, no. 1 (2018): 470-486.

97. Siraj, Md Afjalus, Aaron T. Jacobs, and Ghee T. Tan. "Altersolanol B, a fungal tetrahydroanthraquinone, inhibits the proliferation of estrogen receptor-expressing (ER+) human breast adenocarcinoma by modulating PI3K/AKT, p38/ERK MAPK and associated signaling pathways." *Chemico-Biological Interactions* 359 (2022): 109916.

98. Mantovani, Alberto, Paola Allavena, Antonio Sica, and Frances Balkwill. "Cancer-related inflammation." *nature* 454, no. 7203 (2008): 436-444.

99. Nobili, Stefania, Donatella Lippi, Ewa Witort, Martino Donnini, Letizia Bausi, Enrico Mini, and Sergio Capaccioli. "Natural compounds for cancer treatment and prevention." *Pharmacological research* 59, no. 6 (2009): 365-378.

100. Tanwar, Ankur Kumar, Neha Dhiman, Amit Kumar, and Vikas Jaitak. "Engagement of phytoestrogens in breast cancer suppression: Structural classification and mechanistic approach." *European Journal of Medicinal Chemistry* 213 (2021): 113037.

101. Ayissi, Vincent B. Owona, Azadeh Ebrahimi, and Hermann Schluesenner. "Epigenetic effects of natural polyphenols: A focus on SIRT1-mediated mechanisms." *Molecular nutrition & food research* 58, no. 1 (2014): 22-32.

102. Yahfoufi, Nour, Nawal Alsadi, Majed Jambi, and Chantal Matar. "The immunomodulatory and anti-inflammatory role of polyphenols." *Nutrients* 10, no. 11 (2018): 1618.

103. Childs, Bennett G., Martina Gluscevic, Darren J. Baker, Remi-Martin Laberge, Dan Marquess, Jamie Dananberg, and Jan M. Van Deursen. "Senescent cells: an emerging target for diseases of ageing." *Nature reviews Drug discovery* 16, no. 10 (2017): 718-735.

104. Ouyang, L., Y. Luo, M. Tian, S-Y. Zhang, R. Lu, J-H. Wang, R. Kasimu, and X. Li. "Plant natural products: from traditional compounds to new emerging drugs in cancer therapy." *Cell proliferation* 47, no. 6 (2014): 506-515.

105. García-Lafuente, Ana, Eva Guillamón, Ana Villares, Mauricio A. Rostagno, and José Alfredo Martínez. "Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease." *Inflammation research* 58, no. 9 (2009): 537-552.

106. Perri, F., F. Longo, M. Giuliano, F. Sabbatino, G. Favia, F. Ionna, R. Addeo, G. Della Vittoria Scarpati, G. Di Lorenzo, and S. Pisconti. "Epigenetic control of gene expression: Potential implications for cancer treatment." *Critical reviews in oncology/hematology* 111 (2017): 166-172.

107. Momparler, Richard L. "Cancer epigenetics." *Oncogene* 22, no. 42 (2003): 6479-6483.

108. Morbidelli, Lucia, Erika Terzuoli, and Sandra Donnini. "Use of nutraceuticals in angiogenesis-dependent disorders." *Molecules* 23, no. 10 (2018): 2676.

109. Lee, Hye-Rim, Eui-Bae Jeung, Myung-Haing Cho, Tae-Hee Kim, Peter CK Leung, and Kyung-Chul Choi. "Molecular mechanism (s) of endocrine-disrupting chemicals and their potent oestrogenicity in diverse cells and tissues that express oestrogen receptors." *Journal of cellular and molecular medicine* 17, no. 1 (2013): 1-11.

110. Setchell, Kenneth DR. "Soy isoflavones—benefits and risks from nature's selective estrogen receptor modulators (SERMs)." *Journal of the American College of Nutrition* 20, no. sup5 (2001): 354S-362S.

111. Pisoschi, Aurelia Magdalena, and Aneta Pop. "The role of antioxidants in the chemistry of oxidative stress: A review." *European journal of medicinal chemistry* 97 (2015): 55-74.

112. Karthikeyan, Akash, Abey Joseph, and Baiju G. Nair. "Promising bioactive compounds from the marine environment and their potential effects on various diseases." *Journal of Genetic Engineering and Biotechnology* 20, no. 1 (2022): 1-38.

113. Owen, Noel L., and Nicholas Hundley. "Endophytes—the chemical synthesizers inside plants." *Science progress* 87, no. 2 (2004): 79-99.

114. Patwardhan, Bhushan, Dnyaneshwar Warude, Palpu Pushpangadan, and Narendra Bhatt. "Ayurveda and traditional Chinese medicine: a comparative overview." *Evidence-based complementary and alternative medicine* 2 (2005): 465-473.

115. Martins, Ana, Helena Vieira, Helena Gaspar, and Susana Santos. "Marketed marine natural products in the pharmaceutical and cosmeceutical industries: Tips for success." *Marine drugs* 12, no. 2 (2014): 1066-1101.

116. Elekofehinti, Olusola Olalekan, Opeyemi Iwaloye, Femi Olawale, and Esther Opeyemi Ariyo. "Saponins in cancer treatment: Current progress and future prospects." *Pathophysiology* 28, no. 2 (2021): 250-272.

117. Strobel, Gary, Bryn Daisy, Uvidelio Castillo, and James Harper. "Natural products from endophytic microorganisms." *Journal of Natural products* 67, no. 2 (2004): 257-268.

118. Rutledge, Peter J., and Gregory L. Challis. "Discovery of microbial natural products by activation of silent biosynthetic gene clusters." *Nature reviews microbiology* 13, no. 8 (2015): 509-523.

119. Singh, Satendra, Dev Bukhsh Singh, Shivani Singh, Rohit Shukla, Pramod W. Ramteke, and Krishna Misra. "Exploring medicinal plant legacy for drug discovery in post-genomic era." *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences* 89 (2019): 1141-1151.

120. Bandaranayake, Wickramasinghe M. "Quality control, screening, toxicity, and regulation of herbal drugs." *Modern phytomedicine: turning medicinal plants into drugs* (2006): 25-57.

121. Chen, Chaoxiang, Jialin Wang, Mengdi Sun, Jian Li, and Hui-Min David Wang. "Toward the next-generation phyto-nanomedicines: Cell-derived nanovesicles (CDNs) for natural product delivery." *Biomedicine & Pharmacotherapy* 145 (2022): 112416.

122. Eckhardt, Bedrich L., Prudence A. Francis, Belinda S. Parker, and Robin L. Anderson. "Strategies for the discovery and development of therapies for metastatic breast cancer." *Nature reviews Drug discovery* 11, no. 6 (2012): 479-497.

123. Borahay, Mostafa A., Ayman Al-Hendy, Gokhan S. Kilic, and Darren Boehning. "Signaling pathways in leiomyoma: understanding pathobiology and implications for therapy." *Molecular medicine* 21 (2015): 242-256.

124. Szeja, Wieslaw, Grzegorz Grynkiewicz, and Aleksandra Rusin. "Isoflavones, their glycosides and glycoconjugates. Synthesis and biological activity." *Current Organic Chemistry* 21, no. 3 (2017): 218-235.

125. She, Qing-Bai, David B. Solit, Qing Ye, Kathryn E. O'Reilly, Jose Lobo, and Neal Rosen. "The BAD protein integrates survival signaling by EGFR/MAPK and PI3K/Akt kinase pathways in PTEN-deficient tumor cells." *Cancer cell* 8, no. 4 (2005): 287-297.

126. Puthalakath, Ha, and A. Strasser. "Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins." *Cell Death & Differentiation* 9, no. 5 (2002): 505-512.

127. Sagar, S. M., D. Yance, and R. K. Wong. "Natural health products that inhibit angiogenesis: a potential source for investigational new agents to treat cancer—Part 1." *Current Oncology* 13, no. 1 (2006): 14-26.

128. Hou, Jiajie, Michael Karin, and Beicheng Sun. "Targeting cancer-promoting inflammation—have anti-inflammatory therapies come of age?." *Nature reviews Clinical oncology* 18, no. 5 (2021): 261-279.

129. Zappavigna, Silvia, Alessia Maria Cossu, Anna Grimaldi, Marco Bocchetti, Giuseppe Andrea Ferraro, Giovanni Francesco Nicoletti, Rosanna Filosa, and Michele Caraglia. "Anti-inflammatory drugs as anticancer agents." *International journal of molecular sciences* 21, no. 7 (2020): 2605.

130. Gudkov, Sergey V., Ilya N. Shtarkman, Violetta S. Smirnova, Anatoly V. Chernikov, and Vadim I. Bruskov. "Guanosine and inosine display antioxidant activity, protect DNA in vitro from oxidative damage induced by reactive oxygen species, and serve as radioprotectors in mice." *Radiation research* 165, no. 5 (2006): 538-545.

131. Chaudhry, Gul-e-Saba, Abdah Md Akim, Yeong Yik Sung, and Tengku Muhammad Tengku Sifzizul. "Cancer and apoptosis: The apoptotic activity of plant and marine natural products and their potential as targeted cancer therapeutics." *Frontiers in Pharmacology* 13 (2022): 842376.

132. Cojocneanu Petric, Roxana, Cornelia Braicu, Lajos Raduly, Oana Zanoaga, Nicolae Dragos, Paloma Monroig, Dan Dumitrascu, and Ioana Berindan-Neagoe. "Phytochemicals modulate carcinogenic signaling pathways in breast and hormone-related cancers." *OncoTargets and therapy* (2015): 2053-2066.

133. Pan, Min-Hsiung, and Chi-Tang Ho. "Chemopreventive effects of natural dietary compounds on cancer development." *Chemical Society Reviews* 37, no. 11 (2008): 2558-2574.

134. Ni, Min, Yiwen Chen, Elgene Lim, Hallie Wimberly, Shannon T. Bailey, Yuuki Imai, David L. Rimm, X. Shirley Liu, and Myles Brown. "Targeting androgen receptor in estrogen receptor-negative breast cancer." *Cancer cell* 20, no. 1 (2011): 119-131.

135. Parida, Sheetal, and Dipali Sharma. "The microbiome–estrogen connection and breast cancer risk." *Cells* 8, no. 12 (2019): 1642.

136. Bennasroune, Amar, Anne Gardin, Dominique Aunis, Gérard Crémel, and Pierre Hubert. "Tyrosine kinase receptors as attractive targets of cancer therapy." *Critical reviews in oncology/hematology* 50, no. 1 (2004): 23-38.

137. Kang, Nam Joo, Seung Ho Shin, Hyong Joo Lee, and Ki Won Lee. "Polyphenols as small molecular inhibitors of signaling cascades in carcinogenesis." *Pharmacology & therapeutics* 130, no. 3 (2011): 310-324.

138. Moiseeva, Olga, Xavier Deschênes-Simard, Emmanuelle St-Germain, Sebastian Igelmann, Geneviève Huot, Alexandra E. Cadar, Véronique Bourdeau, Michael N. Pollak, and

Gerardo Ferbeyre. "Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-κ B activation." *Aging cell* 12, no. 3 (2013): 489-498.

139. Yahfoufi, Nour, Nawal Alsadi, Majed Jambi, and Chantal Matar. "The immunomodulatory and anti-inflammatory role of polyphenols." *Nutrients* 10, no. 11 (2018): 1618.

140. Signorelli, Paola, and Riccardo Ghidoni. "Resveratrol as an anticancer nutrient: molecular basis, open questions and promises." *The Journal of nutritional biochemistry* 16, no. 8 (2005): 449-466.

141. Sun, Ying, Yang Liu, Xiaoli Ma, and Hao Hu. "The influence of cell cycle regulation on chemotherapy." *International journal of molecular sciences* 22, no. 13 (2021): 6923.

142. Paoli, Paolo, Elisa Giannoni, and Paola Chiarugi. "Anoikis molecular pathways and its role in cancer progression." *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1833, no. 12 (2013): 3481-3498.

143. Casey, Stephanie C., Amedeo Amedei, Katia Aquilano, Asfar S. Azmi, Fabian Benencia, Dipita Bhakta, Alan E. Bilsland et al. "Cancer prevention and therapy through the modulation of the tumor microenvironment." In *Seminars in cancer biology*, vol. 35, pp. S199-S223. Academic Press, 2015.

144. Aspriţoiu, Veronica Mãdãlina, Ileana Stoica, Coralia Bleotu, and Carmen Cristina Diaconu. "Epigenetic regulation of angiogenesis in development and tumors progression: Potential implications for cancer treatment." *Frontiers in Cell and Developmental Biology* 9 (2021): 689962.

145. Yu, Le, Jessica Wei, and Pengda Liu. "Attacking the PI3K/Akt/mTOR signaling pathway for targeted therapeutic treatment in human cancer." In *Seminars in cancer biology*, vol. 85, pp. 69-94. Academic Press, 2022.

146. He, Yan, Miao Miao Sun, Guo Geng Zhang, Jing Yang, Kui Sheng Chen, Wen Wen Xu, and Bin Li. "Targeting PI3K/Akt signal transduction for cancer therapy." *Signal transduction and targeted therapy* 6, no. 1 (2021): 425.

147. Jantan, Ibrahim, Md Areeful Haque, Laiba Arshad, Hemavathy Harikrishnan, Abdi Wira Septama, and Zeti-Azura Mohamed-Hussein. "Dietary polyphenols suppress chronic inflammation by modulation of multiple inflammation-associated cell signaling pathways." *The Journal of Nutritional Biochemistry* 93 (2021): 108634.

148. Muhammad, Naoshad, Darksha Usmani, Mohammad Tarique, Huma Naz, Mohammad Ashraf, Ramesh Raliya, Shams Tabrez et al. "The role of natural products and their multitargeted approach to treat solid cancer." *Cells* 11, no. 14 (2022): 2209.

149. Marinković, Mija, Matilda Šprung, Maja Buljubašić, and Ivana Novak. "Autophagy modulation in cancer: current knowledge on action and therapy." *Oxidative Medicine and Cellular Longevity* 2018 (2018).

150. Khan, Khushbukhat, Cristina Quispe, Zeeshan Javed, Muhammad Javed Iqbal, Haleema Sadia, Shahid Raza, Asma Irshad, Bahare Salehi, Željko Reiner, and Javad Sharifi-Rad. "Resveratrol, curcumin, paclitaxel and miRNAs mediated regulation of PI3K/Akt/mTOR pathway: go four better to treat bladder cancer." *Cancer Cell International* 20 (2020): 1-19.

151. Asgharian, Parina, Abbas Pirpour Tazekand, Kamran Hosseini, Haleh Forouhandeh, Tohid Ghasemnejad, Maryam Ranjbar, Muzaffar Hasan et al. "Potential mechanisms of quercetin in cancer prevention: Focus on cellular and molecular targets." *Cancer cell international* 22, no. 1 (2022): 257.

152. Feitelson, Mark A., Alla Arzumanyan, Rob J. Kulathinal, Stacy W. Blain, Randall F. Holcombe, Jamal Mahajna, Maria Marino et al. "Sustained proliferation in cancer: Mechanisms and novel therapeutic targets." In *Seminars in cancer biology*, vol. 35, pp. S25-S54. Academic Press, 2015.

153. Amin, ARM Ruhul, Phillip A. Karpowicz, Thomas E. Carey, Jack Arbiser, Rita Nahta, Zhuo G. Chen, Jin-Tang Dong et al. "Evasion of anti-growth signaling: A key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds." In *Seminars in cancer biology*, vol. 35, pp. S55-S77. Academic Press, 2015.

154. Tewari, Devesh, Pooja Patni, Anusha Bishayee, Archana N. Sah, and Anupam Bishayee. "Natural products targeting the PI3K-Akt-mTOR signaling pathway in cancer: A novel therapeutic strategy." In *Seminars in cancer biology*, vol. 80, pp. 1-17. Academic Press, 2022.

155. Issinger, Olaf-Georg, and Barbara Guerra. "Phytochemicals in cancer and their effect on the PI3K/AKT-mediated cellular signalling." *Biomedicine & Pharmacotherapy* 139 (2021): 111650.

156. Rahman, Md Mominur, Md Taslim Sarker, Mst Afroza Alam Tumpa, Md Yamin, Tamanna Islam, Moon Nyeo Park, Md Rezaul Islam et al. "Exploring the recent trends in perturbing the cellular signaling pathways in cancer by natural products." *Frontiers in Pharmacology* 13 (2022): 950109.

157. Singh, Brahma N., Sharmila Shankar, and Rakesh K. Srivastava. "Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications." *Biochemical pharmacology* 82, no. 12 (2011): 1807-1821.

158. Almatroodi, Saleh A., Mohammed A. Alsahli, Ahmad Almatroudi, Amit Kumar Verma, Abdulaziz Aloliqi, Khaled S. Allemailem, Amjad Ali Khan, and Arshad Husain Rahmani. "Potential therapeutic targets of quercetin, a plant flavonol, and its role in the therapy of various types of cancer through the modulation of various cell signaling pathways." *Molecules* 26, no. 5 (2021): 1315.

159. Weng, Chia-Jui, and Gow-Chin Yen. "Flavonoids, a ubiquitous dietary phenolic subclass, exert extensive in vitro anti-invasive and in vivo anti-metastatic activities." *Cancer and Metastasis Reviews* 31 (2012): 323-351.

160. Michalkova, Radka, Martin Kello, Zuzana Kudlickova, Maria Gazdova, Ladislav Mirossay, Gabriela Mojzisova, and Jan Mojzis. "Programmed cell death alterations mediated

by synthetic indole chalcone resulted in cell cycle arrest, DNA damage, apoptosis and signaling pathway modulations in breast cancer model." *Pharmaceutics* 14, no. 3 (2022): 503.

161. Khan, Khushbukhat, Cristina Quispe, Zeeshan Javed, Muhammad Javed Iqbal, Haleema Sadia, Shahid Raza, Asma Irshad, Bahare Salehi, Željko Reiner, and Javad Sharifi-Rad. "Resveratrol, curcumin, paclitaxel and miRNAs mediated regulation of PI3K/Akt/mTOR pathway: go four better to treat bladder cancer." *Cancer Cell International* 20 (2020): 1-19.

162. Unlu, Ahmet, Erdinc Nayir, M. Dogukan Kalenderoglu, Onder Kirca, and Mustafa Ozdogan. "Curcumin (Turmeric) and cancer." *J buon* 21, no. 5 (2016): 1050-1060.

163. Chai, Yu-Shuang, Jun Hu, Fan Lei, Yu-Gang Wang, Zhi-Yi Yuan, Xi Lu, Xin-Pei Wang et al. "Effect of berberine on cell cycle arrest and cell survival during cerebral ischemia and reperfusion and correlations with p53/cyclin D1 and PI3K/Akt." *European journal of pharmacology* 708, no. 1-3 (2013): 44-55.

164. Udenigwe, Chibuike C., Vanu R. Ramprasath, Rotimi E. Aluko, and Peter JH Jones. "Potential of resveratrol in anticancer and anti-inflammatory therapy." *Nutrition reviews* 66, no. 8 (2008): 445-454.

165. Muhammad, Naoshad, Darksha Usmani, Mohammad Tarique, Huma Naz, Mohammad Ashraf, Ramesh Raliya, Shams Tabrez et al. "The role of natural products and their multitargeted approach to treat solid cancer." *Cells* 11, no. 14 (2022): 2209.

166. Yang, H., K. Landis-Piwowar, T. H Chan, and Q. P Dou. "Green tea polyphenols as proteasome inhibitors: implication in chemoprevention." *Current cancer drug targets* 11, no. 3 (2011): 296-306.

167. Wang, Man, Fei Yu, Yuan Zhang, Wenguang Chang, and Meng Zhou. "The effects and mechanisms of flavonoids on cancer prevention and therapy: focus on gut microbiota." *International Journal of Biological Sciences* 18, no. 4 (2022): 1451.

168. Sharifi-Rad, Javad, Cristina Quispe, Muhammad Imran, Abdur Rauf, Muhammad Nadeem, Tanweer Aslam Gondal, Bashir Ahmad et al. "Genistein: an integrative overview of its mode of action, pharmacological properties, and health benefits." *Oxidative medicine and cellular longevity* 2021 (2021).

169. Hussain, Yaseen, Lubna Islam, Haroon Khan, Rosanna Filosa, Michael Aschner, and Saba Javed. "Curcumin–cisplatin chemotherapy: A novel strategy in promoting chemotherapy efficacy and reducing side effects." *Phytotherapy Research* 35, no. 12 (2021): 6514-6529.

170. Chen, Wei-Chih, Ying-An Lai, Ying-Chao Lin, Jui-Wen Ma, Li-Fen Huang, Ning-Sun Yang, Chi-Tang Ho, Sheng-Chu Kuo, and Tzong-Der Way. "Curcumin suppresses doxorubicin-induced epithelial–mesenchymal transition via the inhibition of TGF-β and PI3K/AKT signaling pathways in triple-negative breast Cancer cells." *Journal of agricultural and food chemistry* 61, no. 48 (2013): 11817-11824.

171. Lovly, Christine M., Johannes M. Heuckmann, Elisa de Stanchina, Heidi Chen, Roman K. Thomas, Chris Liang, and William Pao. "Insights into ALK-driven cancers revealed through

development of novel ALK tyrosine kinase inhibitors." *Cancer research* 71, no. 14 (2011): 4920-4931.

172. Yuan, Yeqin, Huizhi Long, Ziwei Zhou, Yuting Fu, and Binyuan Jiang. "PI3K–AKT-Targeting breast cancer treatments: Natural products and synthetic compounds." *Biomolecules* 13, no. 1 (2023): 93.

173. Patel, Sita Sharan, Ashish Acharya, R. S. Ray, Ritesh Agrawal, Ramsaneh Raghuwanshi, and Priyal Jain. "Cellular and molecular mechanisms of curcumin in prevention and treatment of disease." *Critical reviews in food science and nutrition* 60, no. 6 (2020): 887-939.

174. Morita, Yoshihiro, Macall Leslie, Hiroyasu Kameyama, David E. Volk, and Takemi Tanaka. "Aptamer therapeutics in cancer: current and future." *Cancers* 10, no. 3 (2018): 80.

175. Islam, Md Rezaul, Fahadul Islam, Mohamed H. Nafady, Muniya Akter, Saikat Mitra, Rajib Das, Humaira Urmee et al. "Natural small molecules in breast cancer treatment: understandings from a therapeutic viewpoint." *Molecules* 27, no. 7 (2022): 2165.

176. Chhichholiya, Yogita, Malayil Ruthuparna, Harini Velagaleti, and Anjana Munshi. "Brain metastasis in breast cancer: focus on genes and signaling pathways involved, blood–brain barrier and treatment strategies." *Clinical and Translational Oncology* 25, no. 5 (2023): 1218-1241.

177. Garcia-Recio, Susana, Gemma Fuster, Patricia Fernandez-Nogueira, Eva M. Pastor-Arroyo, So Yeon Park, Cristina Mayordomo, Elisabet Ametller et al. "Substance P autocrine signaling contributes to persistent HER2 activation that drives malignant progression and drug resistance in breast cancer." *Cancer research* 73, no. 21 (2013): 6424-6434.

178. Golonko, Aleksandra, Hanna Lewandowska, Renata Świsłocka, U. T. Jasińska, Waldemar Priebe, and Włodzimierz Lewandowski. "Curcumin as tyrosine kinase inhibitor in cancer treatment." *European Journal of Medicinal Chemistry* 181 (2019): 111512.

179. Papa, Salvatore, Pui Man Choy, and Concetta Bubici. "The ERK and JNK pathways in the regulation of metabolic reprogramming." *Oncogene* 38, no. 13 (2019): 2223-2240.

180. Khan, Muhammad, Amara Maryam, He Zhang, Tahir Mehmood, and Tonghui Ma. "Killing cancer with platycodin D through multiple mechanisms." *Journal of cellular and molecular medicine* 20, no. 3 (2016): 389-402.

181. Jha, Saurabh Kumar, Niraj Kumar Jha, Rohan Kar, Rashmi K. Ambasta, and Pravir Kumar. "p38 MAPK and PI3K/AKT signalling cascades inParkinson's disease." *International journal of molecular and cellular medicine* 4, no. 2 (2015): 67.

182. Davis, Cindy D., and John Milner. "Frontiers in nutrigenomics, proteomics, metabolomics and cancer prevention." *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 551, no. 1-2 (2004): 51-64.

183. Gupta, Jalaj, and Angel R. Nebreda. "Roles of p38α mitogen-activated protein kinase in mouse models of inflammatory diseases and cancer." *The FEBS journal* 282, no. 10 (2015): 1841-1857.

184. Hung, Sze Wan, Ruizhe Zhang, Zhouyurong Tan, Jacqueline Pui Wah Chung, Tao Zhang, and Chi Chiu Wang. "Pharmaceuticals targeting signaling pathways of endometriosis as potential new medical treatment: A review." *Medicinal research reviews* 41, no. 4 (2021): 2489-2564.

185. Nandakumar, Vijayalakshmi, Tripti Singh, and Santosh K. Katiyar. "Multi-targeted prevention and therapy of cancer by proanthocyanidins." *Cancer letters* 269, no. 2 (2008): 378-387.

186. Almatroodi, Saleh A., Ahmad Almatroudi, Amjad Ali Khan, Fahad A. Alhumaydhi, Mohammed A. Alsahli, and Arshad Husain Rahmani. "Potential therapeutic targets of epigallocatechin gallate (EGCG), the most abundant catechin in green tea, and its role in the therapy of various types of cancer." *Molecules* 25, no. 14 (2020): 3146.

187. Weng, Chia-Jui, and Gow-Chin Yen. "Flavonoids, a ubiquitous dietary phenolic subclass, exert extensive in vitro anti-invasive and in vivo anti-metastatic activities." *Cancer and Metastasis Reviews* 31 (2012): 323-351.

188. Al-Khayri, Jameel M., Gandasi Ravikumar Sahana, Praveen Nagella, Biljo V. Joseph, Fatima M. Alessa, and Muneera Q. Al-Mssallem. "Flavonoids as potential anti-inflammatory molecules: A review." *Molecules* 27, no. 9 (2022): 2901.

189. Brglez Mojzer, Eva, Maša Knez Hrnčič, Mojca Škerget, Željko Knez, and Urban Bren. "Polyphenols: Extraction methods, antioxidative action, bioavailability and anticarcinogenic effects." *Molecules* 21, no. 7 (2016): 901.

190. Wang, Cong, Wenpei Fan, Zijian Zhang, Yu Wen, Li Xiong, and Xiaoyuan Chen. "Advanced nanotechnology leading the way to multimodal imaging-guided precision surgical therapy." *Advanced Materials* 31, no. 49 (2019): 1904329.

191. Souri, Mohammad, M. Soltani, Farshad Moradi Kashkooli, Mohammad Kiani Shahvandi, Mohsen Chiani, Fatemeh Sadat Shariati, Mohammad Reza Mehrabi, and Lance L. Munn. "Towards principled design of cancer nanomedicine to accelerate clinical translation." *Materials Today Bio* 13 (2022): 100208.

192. Al Mamun, Abdullah, Mohammad Abu Sufian, Md Sahab Uddin, Dewan Md Sumsuzzman, Philippe Jeandet, Mohammad Safiqul Islam, Hong-Jie Zhang, Ah-Ng Kong, and Md Shahid Sarwar. "Exploring the role of senescence inducers and senotherapeutics as targets for anticancer natural products." *European Journal of Pharmacology* 928 (2022): 174991.

193. Afroze, Nazia, Sreepoorna Pramodh, Jasmin Shafarin, Khuloud Bajbouj, Mawieh Hamad, Madhumitha Kedhari Sundaram, Shafiul Haque, and Arif Hussain. "Fisetin deters cell proliferation, induces apoptosis, alleviates oxidative stress and inflammation in human cancer cells, HeLa." *International Journal of Molecular Sciences* 23, no. 3 (2022): 1707.

194. Jiang, Ai-Jun, Guan Jiang, Lian-Tao Li, and Jun-Nian Zheng. "Curcumin induces apoptosis through mitochondrial pathway and caspases activation in human melanoma cells." *Molecular biology reports* 42 (2015): 267-275.

195. Kwakye, Akosua Kotaa, Sylvanus Kampo, Jiaxin Lv, Muhammad Noman Ramzan, Seidu A. Richard, Aglais Arredondo Falagán, Jerry Agudogo, Evans Atito-Narh, Qiu Yan, and Qing-Ping Wen. "Levobupivacaine inhibits proliferation and promotes apoptosis of breast cancer cells by suppressing the PI3K/Akt/mTOR signalling pathway." *BMC research notes* 13 (2020): 1-8.

196. Man, Gene Chi Wai, Jianzhang Wang, Yi Song, Jack Ho Wong, Yu Zhao, Tat San Lau, Kam Tong Leung et al. "Therapeutic potential of a novel prodrug of green tea extract in induction of apoptosis via ERK/JNK and Akt signaling pathway in human endometrial cancer." *BMC cancer* 20 (2020): 1-14.

197. Wu, Liwei, Jingjing Li, Tong Liu, Sainan Li, Jiao Feng, Qiang Yu, Jie Zhang et al. "Quercetin shows anti-tumor effect in hepatocellular carcinoma LM3 cells by abrogating JAK2/STAT3 signaling pathway." *Cancer medicine* 8, no. 10 (2019): 4806-4820.

198. Imran, Muhammad, Farhan Saeed, Syed Amir Gilani, Mohammad Ali Shariati, Ali Imran, Muhammad Afzaal, Muhammad Atif, Tabussam Tufail, and Faqir M. Anjum. "Fisetin: An anticancer perspective." *Food Science & Nutrition* 9, no. 1 (2021): 3-16.

199. Majidinia, Maryam, Javad Aghazadeh, Rana Jahanban-Esfahlani, and Bahman Yousefi. "The roles of Wnt/β-catenin pathway in tissue development and regenerative medicine." *Journal of cellular physiology* 233, no. 8 (2018): 5598-5612.

200. Varghese, Elizabeth, Samson Mathews Samuel, Mariam Abotaleb, Sohaila Cheema, Ravinder Mamtani, and Dietrich Büsselberg. "The “Yin and Yang” of natural compounds in anticancer therapy of triple-negative breast cancers." *Cancers* 10, no. 10 (2018): 346.

201. Jingjie, Wang, and Shen Jun. "Gut vascular barrier in the pathogenesis and resolution of Crohn's disease: A novel link from origination to therapy." *Clinical Immunology* (2023): 109683.

202. Juhl IV, Otto J., Anna-Blessing Merife, Yue Zhang, Christopher A. Lemmon, and Henry J. Donahue. "Hydroxyapatite particle density regulates osteoblastic differentiation through β-catenin translocation." *Frontiers in Bioengineering and Biotechnology* 8 (2021): 591084.

203. Chen, Jiayu, Meng Wang, Yuancai Xiang, Xufang Ru, Yonggang Ren, Xiping Liu, Lu Qiu, and Yiguo Zhang. "Nrf1 is endowed with a dominant tumor-repressing effect onto the Wnt/β-catenin-dependent and Wnt/β-catenin-independent signaling networks in the human liver cancer." *Oxidative medicine and cellular longevity* 2020 (2020).

204. Sferrazza, Gianluca, Marco Corti, Gloria Brusotti, Pasquale Pierimarchi, Caterina Temporini, Annalucia Serafino, and Enrica Calleri. "Nature-derived compounds modulating Wnt/β-catenin pathway: A preventive and therapeutic opportunity in neoplastic diseases." *Acta Pharmaceutica Sinica B* 10, no. 10 (2020): 1814-1834.

205. Block, Keith I., Charlotte Gyllenhaal, Leroy Lowe, Amedeo Amedei, ARM Ruhul Amin, Amr Amin, Katia Aquilano et al. "Designing a broad-spectrum integrative approach for cancer prevention and treatment." In *Seminars in cancer biology*, vol. 35, pp. S276-S304. Academic Press, 2015.

206. Hiremath, Ishita S., Arul Goel, Sudha Warrier, Alan Prem Kumar, Gautam Sethi, and Manoj Garg. "The multidimensional role of the Wnt/β-catenin signaling pathway in human malignancies." *Journal of Cellular Physiology* 237, no. 1 (2022): 199-238.

207. Farooqi, Ammad Ahmad, Marina Pinheiro, Andreia Granja, Fulvia Farabegoli, Salette Reis, Rukset Attar, Uteuliyev Yerzhan Sabitaliyevich, Baojun Xu, and Aamir Ahmad. "EGCG mediated targeting of deregulated signaling pathways and non-coding RNAs in different cancers: Focus on JAK/STAT, Wnt/β-Catenin, TGF/SMAD, NOTCH, SHH/GLI, and TRAIL mediated signaling pathways." *Cancers* 12, no. 4 (2020): 951.

208. Leow, Pay-Chin, Quan Tian, Zhan-Yuin Ong, Zheng Yang, and Pui-Lai Rachel Ee. "Antitumor activity of natural compounds, curcumin and PKF118-310, as Wnt/β-catenin antagonists against human osteosarcoma cells." *Investigational new drugs* 28 (2010): 766-782.

209. Bajalia, Essa M., Farah B. Azzouz, Danielle A. Chism, Derrek M. Giansiracusa, Carina G. Wong, Kristina N. Plaskett, and Anupam Bishayee. "Phytochemicals for the prevention and treatment of renal cell carcinoma: preclinical and clinical evidence and molecular mechanisms." *Cancers* 14, no. 13 (2022): 3278.

210. Juge, N., R. F. Mithen, and M. Traka. "Molecular basis for chemoprevention by sulforaphane: a comprehensive review." *Cellular and Molecular Life Sciences* 64 (2007): 1105-1127.

211. Shan, Bao-En, Ming-Xia Wang, and Run-qing Li. "Quercetin inhibit human SW480 colon cancer growth in association with inhibition of cyclin D1 and survivin expression through Wnt/β-catenin signaling pathway." *Cancer investigation* 27, no. 6 (2009): 604-612.

212. Verras, Meletios, and Zijie Sun. "Roles and regulation of Wnt signaling and β-catenin in prostate cancer." *Cancer letters* 237, no. 1 (2006): 22-32.

213. Chan, Karen KL, Michelle KY Siu, Yu-xin Jiang, Jing-jing Wang, Thomas HY Leung, and Hextan YS Ngan. "Estrogen receptor modulators genistein, daidzein and ERB-041 inhibit cell migration, invasion, proliferation and sphere formation via modulation of FAK and PI3K/AKT signaling in ovarian cancer." *Cancer cell international* 18 (2018): 1-14.

214. Chen, Hui-Jye, Le-Shiang Hsu, Yu-Ting Shia, Meng-Wei Lin, and Chung-Ming Lin. "The β-catenin/TCF complex as a novel target of resveratrol in the Wnt/β-catenin signaling pathway." *Biochemical pharmacology* 84, no. 9 (2012): 1143-1153.

215. Zhai, Kevin, Manaal Siddiqui, Basma Abdellatif, Alena Liskova, Peter Kubatka, and Dietrich Büsselberg. "Natural compounds in glioblastoma therapy: Preclinical insights, mechanistic pathways, and outlook." *Cancers* 13, no. 10 (2021): 2317.

216. Bi, Zhuofei, Qingjian Li, Xiaoxiao Dinglin, Ying Xu, Kaiyun You, Huangming Hong, Qian Hu et al. "Nanoparticles (NPs)-meditated LncRNA AFAP1-AS1 silencing to block Wnt/β-Catenin signaling pathway for synergistic reversal of radioresistance and effective cancer radiotherapy." *Advanced Science* 7, no. 18 (2020): 2000915.

217. Feitelson, Mark A., Alla Arzumanyan, Rob J. Kulathinal, Stacy W. Blain, Randall F. Holcombe, Jamal Mahajna, Maria Marino et al. "Sustained proliferation in cancer: Mechanisms and novel therapeutic targets." In *Seminars in cancer biology*, vol. 35, pp. S25-S54. Academic Press, 2015.

218. Niedzwiecki, Aleksandra, Bilwa Bhanap, M. Waheed Roomi, and Matthias Rath. "Expanding Metabolic Targets in Cancer by Select Combinations of Vitamin C and EGCG with Different Natural Compounds." *Nutraceuticals in Veterinary Medicine* (2019): 611-624.

219. Abdal Dayem, Ahmed, Hye Yeon Choi, Gwang-Mo Yang, Kyeongseok Kim, Subbroto Kumar Saha, and Ssang-Goo Cho. "The anti-cancer effect of polyphenols against breast cancer and cancer stem cells: molecular mechanisms." *Nutrients* 8, no. 9 (2016): 581.

220. Tsubakihara, Yutaro, and Aristidis Moustakas. "Epithelial-mesenchymal transition and metastasis under the control of transforming growth factor β." *International journal of molecular sciences* 19, no. 11 (2018): 3672.

221. Li, Shih-Hui, Junsheng Fu, Dara Nall Watkins, Rakesh K. Srivastava, and Sharmila Shankar. "Sulforaphane regulates self-renewal of pancreatic cancer stem cells through the modulation of Sonic hedgehog–GLI pathway." *Molecular and cellular biochemistry* 373 (2013): 217-227.

222. Sinha, Sonam, Sonal Sharma, Abhilasha Sharma, Jaykant Vora, and Neeta Shrivastava. "Sulforaphane-cisplatin combination inhibits the stemness and metastatic potential of TNBCs via down regulation of sirtuins-mediated EMT signaling axis." *Phytomedicine* 84 (2021): 153492.

223. Sak, Katrin, and Hele Everaus. "Role of flavonoids in future anticancer therapy by eliminating the cancer stem cells." *Current stem cell research & therapy* 10, no. 3 (2015): 271-282.

224. Talib, Wamidh H., Safa Daoud, Asma Ismail Mahmod, Reem Ali Hamed, Dima Awajan, Sara Feras Abuarab, Lena Hisham Odeh, Samar Khater, and Lina T. Al Kury. "Plants as a source of anticancer agents: From bench to bedside." *Molecules* 27, no. 15 (2022): 4818.

225. Najafi, Masoud, Jamal Majidpoor, Heidar Toolee, and Keywan Mortezaee. "The current knowledge concerning solid cancer and therapy." *Journal of biochemical and molecular toxicology* 35, no. 11 (2021): e22900.

226. Najafi, Masoud, Jamal Majidpoor, Heidar Toolee, and Keywan Mortezaee. "The current knowledge concerning solid cancer and therapy." *Journal of biochemical and molecular toxicology* 35, no. 11 (2021): e22900.

227. Fares, Jawad, Mohamad Y. Fares, Hussein H. Khachfe, Hamza A. Salhab, and Youssef Fares. "Molecular principles of metastasis: a hallmark of cancer revisited." *Signal transduction and targeted therapy* 5, no. 1 (2020): 28.

228. Korzun, Tetiana, Abraham S. Moses, Parham Diba, Ariana L. Sattler, Brennan Olson, Olena R. Taratula, Tanja Pejovic, Daniel L. Marks, and Oleh Taratula. "Development and

Perspectives: Multifunctional Nucleic Acid Nanomedicines for Treatment of Gynecological Cancers." *Small* (2023): 2301776.

229. Rimawi, Mothaffar F., Rachel Schiff, and C. Kent Osborne. "Targeting HER2 for the treatment of breast cancer." *Annual review of medicine* 66 (2015): 111-128.

230. Aggarwal, Bharat B., and Shishir Shishodia. "Molecular targets of dietary agents for prevention and therapy of cancer." *Biochemical pharmacology* 71, no. 10 (2006): 1397-1421.

231. Mohammad, Ramzi M., Irfana Muqbil, Leroy Lowe, Clement Yedjou, Hsue-Yin Hsu, Liang-Tzung Lin, Markus David Siegelin et al. "Broad targeting of resistance to apoptosis in cancer." In *Seminars in cancer biology*, vol. 35, pp. S78-S103. Academic Press, 2015.

232. Derry, Molly Marie, Komal Raina, and Rajesh Agarwal. "Identifying molecular targets of lifestyle modifications in colon cancer prevention." *Frontiers in oncology* 3 (2013): 51352.

233. Weng, Chia-Jui, and Gow-Chin Yen. "Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: phenolic acids, monophenol, polyphenol, and their derivatives." *Cancer treatment reviews* 38, no. 1 (2012): 76-87.

234. Bild, Andrea H., Guang Yao, Jeffrey T. Chang, Quanli Wang, Anil Potti, Dawn Chasse, Mary-Beth Joshi et al. "Oncogenic pathway signatures in human cancers as a guide to targeted therapies." *Nature* 439, no. 7074 (2006): 353-357.

235. Drago, Joshua Z., Shanu Modi, and Sarat Chandarlapaty. "Unlocking the potential of antibody–drug conjugates for cancer therapy." *Nature Reviews Clinical Oncology* 18, no. 6 (2021): 327-344.

236. Hashem, Sheema, Tayyiba Akbar Ali, Sabah Akhtar, Sabah Nisar, Geetanjali Sageena, Shahid Ali, Sharefa Al-Mannai et al. "Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents." *Biomedicine & Pharmacotherapy* 150 (2022): 113054.

237. Wu, Tai-Na, Hui-Ming Chen, and Lie-Fen Shyur. "Current advancements of plant-derived agents for triple-negative breast cancer therapy through deregulating cancer cell functions and reprogramming tumor microenvironment." *International Journal of Molecular Sciences* 22, no. 24 (2021): 13571.

238. Feng, Yixiao, Mia Spezia, Shifeng Huang, Chengfu Yuan, Zongyue Zeng, Linghuan Zhang, Xiaojuan Ji et al. "Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis." *Genes & diseases* 5, no. 2 (2018): 77-106.

239. Manzari, Mandana T., Yosi Shamay, Hiroto Kiguchi, Neal Rosen, Maurizio Scaltriti, and Daniel A. Heller. "Targeted drug delivery strategies for precision medicines." *Nature Reviews Materials* 6, no. 4 (2021): 351-370.

240. Blowman, K., M. Magalhães, M. F. L. Lemos, C. Cabral, and I. M. Pires. "Anticancer properties of essential oils and other natural products." *Evidence-Based Complementary and Alternative Medicine* 2018 (2018).

241. Zhou, Shibin, Claudia Gravekamp, David Bermudes, and Ke Liu. "Tumour-targeting bacteria engineered to fight cancer." *Nature Reviews Cancer* 18, no. 12 (2018): 727-743.

242. Mut-Salud, Nuria, Pablo Juan Álvarez, Jose Manuel Garrido, Esther Carrasco, Antonia Aránega, and Fernando Rodríguez-Serrano. "Antioxidant intake and antitumor therapy: toward nutritional recommendations for optimal results." *Oxidative Medicine and Cellular Longevity* 2016 (2016).

243. Li, Yvonne Y., and Steven JM Jones. "Drug repositioning for personalized medicine." *Genome medicine* 4 (2012): 1-14.

244. Zhou, Xian, Chun-Guang Li, Dennis Chang, and Alan Bensoussan. "Current status and major challenges to the safety and efficacy presented by Chinese herbal medicine." *Medicines* 6, no. 1 (2019): 14.

245. Lee, Jun H., and Anjan Nan. "Combination drug delivery approaches in metastatic breast cancer." *Journal of drug delivery* 2012 (2012).

246. Estrela, Jose M., Salvador Mena, Elena Obrador, Maria Benlloch, Gloria Castellano, Rosario Salvador, and Ryan W. Dellinger. "Polyphenolic phytochemicals in cancer prevention and therapy: bioavailability versus bioefficacy." *Journal of medicinal chemistry* 60, no. 23 (2017): 9413-9436.

247. Akhurst, Rosemary J., and Akiko Hata. "Targeting the TGFβ signalling pathway in disease." *Nature reviews Drug discovery* 11, no. 10 (2012): 790-811.

248. Lambert, Martin, and Dieter Naber. "Current issues in schizophrenia: overview of patient acceptability, functioning capacity and quality of life." *CNS drugs* 18, no. Suppl 2 (2004): 5-17.

249. Block, Keith I., Beverly Burns, Andrea J. Cohen, Adrian S. Dobs, Suzanne M. Hess, and Andrew Vickers. "Point-counterpoint: using clinical trials for the evaluation of integrative cancer therapies." *Integrative Cancer Therapies* 3, no. 1 (2004): 66-81.

250. Zhang, Zhe, Li Zhou, Na Xie, Edouard C. Nice, Tao Zhang, Yongping Cui, and Canhua Huang. "Overcoming cancer therapeutic bottleneck by drug repurposing." *Signal transduction and targeted therapy* 5, no. 1 (2020): 113.

251. Sambi, Manpreet, Leila Bagheri, and Myron R. Szewczuk. "Current challenges in cancer immunotherapy: multimodal approaches to improve efficacy and patient response rates." *Journal of oncology* 2019 (2019).

252. Chae, Young Kwang, Alan P. Pan, Andrew A. Davis, Sandip P. Patel, Benedito A. Carneiro, Razelle Kurzrock, and Francis J. Giles. "Path toward precision oncology: review of targeted therapy studies and tools to aid in defining “actionability” of a molecular lesion and patient management support." *Molecular cancer therapeutics* 16, no. 12 (2017): 2645-2655.

253. Viktorsson, Kristina, Thorsten Rieckmann, Maximilian Fleischmann, Markus Diefenhardt, Stephanie Hehlgans, and Franz Rödel. "Advances in molecular targeted therapies

to increase efficacy of (chemo) radiation therapy." *Strahlentherapie und Onkologie* (2023): 1-19.

254. Sharma H, Pathak R, Biswas D. Unveiling the Therapeutic Potential of Modern Probiotics in Addressing Neurodegenerative Disorders: A Comprehensive Exploration, Review and Future Perspectives on Intervention Strategies. Curr Psychiatry Res Rev [Internet]. 2024 May 29;20. doi: 10.2174/0126660822304321240520075036.

255. Kapoor DU, Sharma H, Maheshwari R, Pareek A, Gaur M, Prajapati BG, et al. Konjac Glucomannan: A comprehensive review of its extraction, health benefits, and pharmaceutical applications. Carbohydr Polym [Internet]. 2024;122266. https://doi.org/10.1016/j.carbpol.2024.122266

256. Chandra P, Ali Z, Fatima N, Sharma H, Sachan N, Sharma KK, et al. Shankhpushpi (Convolvulus pluricaulis): Exploring its Cognitive Enhancing Mechanisms and Therapeutic Potential in Neurodegenerative Disorders. Curr Bioact Compd [Internet]. 2024 Apr 29;20. DOI: 10.2174/0115734072292339240416095600

257. Kumar P, Sharma H, Singh A, Durgapal S, Kukreti G, Bhowmick M, et al. Targeting the Interplay of Proteins through PROTACs for Management Cancer and Associated Disorders. Curr Cancer Ther Rev [Internet]. 2024 Apr 29;20. Doi:10.2174/0115733947304806240417092449

258. Sharma H, Chandra P. Effects of natural remedies on memory loss and Alzheimer's disease. Afr.J.Bio.Sc. 6(7) (2024).187-211. https://doi.org/ 10.33472/AFJBS.6.7.2024.187-211

259. Halagali P, Inamdar A, Singh J, Anand A, Sadhu P, Pathak R, et al. Phytochemicals, Herbal Extracts, and Dietary Supplements for Metabolic Disease Management. Endocrine, Metab Immune Disord - Drug Targets [Internet]. 2024 Apr 26;24. DOI: 10.2174/0118715303287911240409055710

260. Das S, Mukherjee T, Mohanty S, Nayak N, Mal P, Ashique S, et al. Impact of NF-κB Signaling and Sirtuin-1 Protein for Targeted Inflammatory Intervention. Curr Pharm Biotechnol [Internet]. 2024 Apr 17;25. DOI:10.2174/0113892010301469240409082212

261. Sharma H, Kaushik M, Goswami P, Sreevani S, Chakraborty A, Ashique S, et al. Role of miRNAs in Brain Development. MicroRNA. 2024 Apr 2;13. https://doi.org/10.2174/0122115366287127240322054519

262. Ashique S, Bhowmick M, Pal R, Khatoon H, Kumar P, Sharma H, Garg A, Kumar S, Das U. Multi drug resistance in colorectal cancer-approaches to overcome, advancements and future success. Advances in Cancer Biology-Metastasis. 2024 Jan 12:100114. https://doi.org/10.1016/j.adcanc.2024.100114

263. Ashique S, Pal R, Sharma H, Mishra N, Garg A. Unraveling the Emerging Niche Role of Extracellular Vesicles (EVs) in Traumatic Brain Injury (TBI). CNS & Neurological Disorders Drug Targets. 2024 Feb 13. doi: 10.2174/0118715273288155240201065041

264. Kumar P, Pandey S, Ahmad F, Verma A, Sharma H, Ashique S, et al. Carbon Nanotubes: A Targeted Drug Delivery against Cancer Cell. Curr Nanosci. 2023 Nov 8;9:1–31. doi: 10.2174/0115734137271865231105070727

265. Sharma H, Chandra P, Verma A, Pandey SN, Kumar P, Sigh A. Therapeutic approaches of nutraceuticals in the prevention of neurological disorders. Eur Chem Bull. 2023;12(5):1575 – 1596. doi: - 10.48047/ecb/2023.12.si5a.038

266. Sharma H, Chandra P. Challenges and Future Prospects: A Benefaction of Phytoconstituents on Molecular Targets Pertaining to Alzheimer's Disease. Int J Pharm Investig. 2023 Dec 27;14(1):117–26. doi:10.5530/ijpi.14.1.15

267. Sharma H, Pathak R, Jain S, Bhandari M, Mishra R, Reena K, Varshney P. Ficus racemosa L: A review on its important medicinal uses, phytochemicals and biological activities. Journal of Population Therapeutics and Clinical Pharmacology. 2023 Jul 15;30(17):213-27. doi: 10.47750/jptcp.2023.30.17.018

268. Singh LP, Gugulothu S, Perusomula R, Mishra A, Bhavani PD, Singh S, Sharma H, Dwivedi M. Synthesis of Some Tetrazole and Thiazolidine-4-One Derivatives of Schiff base by using Ionic Liquids as Catalyst and Evaluation of their Antifungal and Antibacterial Activity. Eur. Chem. Bull. 2023, 12 (Special Issue8),281-297.

269. Pathak, Rashmi & Sharma, Himanshu & Nogai, Lipi & Bhandari, Maulshree & Koli, Manju & Mishra, Riya & Kumar, N. A Brief Review on Pathogenesis, Transmission and Management of Monkeypox Virus Outbreaks. Bull. Environ. Pharmacol. Life Sci. 2023, 12 (4), 244–256.

270. Sharma H, Bhattacharya V, Bhatt A, Garg S, Chaurasia G, Akram W, Sharma K, Mandal S. "Optimization of formulation by box Behnken and *in-vitro* studies of emulsified gel containing zaltoprofen for the management of arthritis" in Eur. Chem. Bull. 2023,12(Special Issue 4),11734-11744.

271. Koli M, Nogai L, Bhandari M, Mishra R, Pathak R, Sharma H. Formulation And Evaluation Of Berberine Hydrochloride Film Coated Tablet. Journal of Pharmaceutical Negative Results. 2023 Feb 10:3439-49. doi: 10.47750/pnr.2023.14.02.403

272. Dwivedi M, Jha KK, Pandey S, Sachan A, Sharma H, Dwivedi SK. Formulation and Evaluation of Herbal Medicated Chocolate in Treatment of Intestinal Worms and Related Problems. IJFANS. 2022, 11 (2), 1426- 1439.

273. Sharma H, Pathak R, Kumar N, Nogai L, Mishra R, Bhandari M, Koli M, Pandey P. Endocannabinoid System: Role in Depression, Recompense, And Pain Control. Journal of Survey in Fisheries Sciences. 2023 Apr 17;10(4S):2743-51. https://doi.org/10.17762/sfs.v10i4S.1655

274. Sharma H, Pathak R, Saxena D, Kumar N. "Emerging role of non-coding RNA'S: human health and diseases" in GIS. 2022, 9 (7) 2022-2050.

275. Sharma H, Rani T, Khan S. An Insight into Neuropathic Pain: A Systemic and up-to-Date Review. IJPSR 2023, 14(2):607–621. http://dx.doi.org/10.13040/IJPSR.0975-8232.14(2).607-21

276. Pandey P, Kumar N, Kaur T, Saini S, Sharma H. Antidiabetic Activity of Caesalpinia Bonducella Leaves of Hydro Alcoholic Extracts in Albino Rats. YMER. 2022, 7(21), 840-846.

277. Pathak R, Sharma H, Kumar N. A Brief Review on Anthocephalus cadamba. Acta Scientific Pharmacology. 2022 May;3(5).

278. Sharma S, Dinda SC, Sharma H, Matrix types drug delivery system for sustained release: a review, ASIO Journal of Drug Delivery (ASIO-JDD), 2022, 6(1): 01-08. https://doi-ds.org/doilink/03.2022-65678198/ASIO-JDD/10.2016-21915953/2022/V6I1/920

279. Sharma H, Pathak R. A REVIEW ON PRELIMENARY PHYTOCHEMICAL SCREENING OF CURCUMA LONGA LINN. J Pharma Herbal Med Res (ASIO-JPHMR). 2021;7(2):24-27. https://doi-ds.org/doilink/10.2021-97622886/ASIO_JPHMR/ 10.2016-19146535/V7/I2/460

280. Pathak R, Sharma H. A review on medicinal uses of Cinnamomum verum (Cinnamon). Journal of Drug Delivery and Therapeutics. 2021 Dec 15;11(6-S):161-6. http://dx.doi.org/10.22270/jddt.v11i6-S.5145

281. Sharma H, Pande M, Jha KK, Hyperuricemia: a risk factor beyond gout, ASIO Journal of Pharmaceutical & Herbal Medicines Research (ASIO-JPHMR), 2020, 6(1), 42-49. http://doi-ds.org/doilink/06.2020-25164442/

282. Sharma H, Singh S, Jha KK, Treatment and recommendations for homeless patients with hypertension, hyperlipidemia & heart failure-a review, ASIO Journal of Experimental Pharmacology & Clinical Research (ASIO-JEPCR), 2020, 6(1): 24-32. http://doi-ds.org/doilink/07.2020-72295186/

283. Sharma H, Rachamalla HK, Mishra N, Chandra P, Pathak R, Ashique S. Introduction to Exosome and Its Role in Brain Disorders BT - Exosomes Based Drug Delivery Strategies for Brain Disorders. In: Mishra N, Ashique S, Garg A, Chithravel V, Anand K, editors. Singapore: Springer Nature Singapore; 2024. p. 1–35. Available from: https://doi.org/10.1007/978-981-99-8373-5_1

284. Sharma H, Tyagi SJ, Chandra P, Verma A, Kumar P, Ashique S, et al. Role of Exosomes in Parkinson's and Alzheimer's Diseases BT - Exosomes Based Drug Delivery Strategies for Brain Disorders. In: Mishra N, Ashique S, Garg A, Chithravel V, Anand K, editors. Singapore: Springer Nature Singapore; 2024. p. 147–82. Available from: https://doi.org/10.1007/978-981-99-8373-5_6

285. Kumar P, Sharma H, Singh A, Pandey SN, Chandra P. Correlation Between Exosomes and Neuro-inflammation in Various Brain Disorders BT - Exosomes Based Drug Delivery Strategies for Brain Disorders. In: Mishra N, Ashique S, Garg A, Chithravel V, Anand K, editors. Singapore: Springer Nature Singapore; 2024. p. 273–302. Available from: https://doi.org/10.1007/978-981-99-8373-5_11

286. Pathak R, Kaur V, Sharma S, Bhandari M, Mishra R, Saxena A, et al. Pazopanib: Effective monotherapy for precise cancer treatment, targeting specific mutations and tumors. 2024;6(9):1311–30. https://doi.org/ 10.33472/AFJBS.6.9.2024.1311-1330

287. Shetty SS, Halagali P, Johnson AP, Spandana KA, Gangadharappa HV. Oral insulin delivery: Barriers, strategies, and formulation approaches: A comprehensive review. International Journal of Biological Macromolecules. 2023 May 31:125114.

288. Soundarya R, Halagali P, Preethi S, Vikram HP, Mehdi S, Singadi R. Quality By Design (QBD) approach in processing of nanoparticles loading antifungal drugs. Journal of Coastal Life Medicine. 2023 Feb 7;11:279-90.

289. Bardeesy N, DePinho RA. Pancreatic cancer biology and genetics. Nature Reviews Cancer. 2002 Dec 1;2(12):897-909.

290. Gandraju A, Vishnu Vardh R, Vardhan PV, Mohsen MM, Halagali P, Girish MS, Kumar H. Access Control and Password Security Management in Pharmaceutical Industry. Journal of Survey in Fisheries Sciences. 2023 Mar 24;10(4S):861-70.

291. Rane S, Adhyapak A, Gharge S, Koli R, Singadi R, Halagali P. UV and HPTLC-Based Approaches towards Rutin Determination in Abutilon theophrasti Extract. Journal of Pharmaceutical Sciences and Research. 2022 Jul 1;14(7):790-4.

292. M P Venkatesh, Ashish Kumar Sahoo, Amit B Patil, Praveen Halagali, 2023. Current advances in dry eye disease diagnosis and treatment. Journal of medical pharmaceutical and allied sciences, V 12 - I 2, Pages - 5724 – 5724. Doi: 10.55522/jmpas.V12I2.4952.

293. James A, Halagali P, Jafar M, Sanu J, Bharadwaj RK, Shaju B, et al. Formulation and Evaluation of Fumaria parviflora Loaded Oil in Water Emulsion-Based Cream. Int. J. Pharm. Investigation. 2024;14(2):493-503.

294. Halagali P, Singadi R, Arjun HR, Rakshanaa GS, Nair SP, Halagali P, et al. Role of Traditional Plant Compounds in the Treatment of Neuropsychiatric Diseases. Int. J. Pharm. Investigation. 2024;14(1):48-54.

295. HR A, Halagali P, Tausif M, UR R, Rakshanaa GS. Type3c Diabetes Mellitus. International Journal of Pharmaceutical Investigation. 2023 Oct 1;13(4).

296. CP Y, kumar Desai K, Halagali P, Gangadharappa HV. Water Qualification in Pharmaceutical Industry. Journal of Coastal Life Medicine. 2023 Jan 11;11:1918-32.

297. Gowda CU, Gaganashree TV, Priyanka LG, Roy K, Halagali P, Angolkar M, Preethi S. Regulatory Aspects Concerning Generic Drugs Approval In “Brics” Countries”. Journal of Survey in Fisheries Sciences. 2023 Mar 26;10(4S):915-26.

298. Vaishnavi Jahagirdar SM, Krishna KL, Palaksha S, Shariff A, Doddawad VG, Halagali P, Tausif YM. An Overview Of EGCG And Its Potential Effects On Breast Cancer Cells. Journal of Pharmaceutical Negative Results. 2023 Jan 25:800-6.

299. Shivaprasad GD, Shalagali P, Koliwad VV, Savadatti KI. Novel Scaffolds Benzimidazole: AReview.

300. Halagali P, Bolmal UB, Jain DP, Singadi R. FORMULATION DEVELOPMENT AND EVALUATION OF MEDICATED CANDY CONTAINING PARACETAMOL FOR NEONATE.Halagali P, Bolmal UB, Patil AS. DEVELOPMENT AND EVALUATION OF PARACETAMOL LOZENGES.

301. Deshpande PS, Kumar H. RECENT ADVANCEMENTS IN THE DEVELOPMENT OF PROBIOTICS AS PHARMACEUTICALS: A REVIEW.

302. Osmani RA. Functionalized Polysaccharides Based Hydrogels: Application in Tissue Engineering and Regenerative Medicines.

303. Singadi R, Maste MM, Gharge S, Halagali P, Bhandurge P, Suryawanshi SS. Physico-chemical investigation and characterization of Fumaria parviflora lam.

304. Arjun HR, Tausi YM, Halagali P, Paramakrishnan N, Rakshith UR. Role of Stem Cells in the Management of Type-I Diabetes Mellitus. Indian J of Pharmaceutical Education and Research. 2023;57(4):951-5

305. Udigala Renukaprasad Rakshith, Salini Parameswaran Nair, Arjun Hunsur Ranganath, Praveen Halagali Drug Interactions: Mechanisms, Assessment and Management Strategies Journal of Young Pharmacists, 2024; 16(3):1-9.