

Herbal Drugs in Cancer Therapy: Current Trends & Future Perspectives

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Abstract:- The potential of herbal medicines as complementary or alternative therapies has drawn a lot of attention in the field of cancer therapy. This review paper offers a thorough analysis of the most recent developments as well as potential directions for the use of herbal medications in cancer treatment. We draw attention to the extensive history of conventional herbal remedies while highlighting the mounting body of research demonstrating their potential as anticancer treatments. The review delves into the primary processes by which herbal medications work, including their anti-inflammatory, antioxidant, and immunomodulatory properties.

We also discuss the difficulties and prospects of incorporating herbal remedies into conventional oncology practice, emphasizing the need for safety, standardization, and regulatory concerns.

In conclusion, we provide an overview of prospective herbal candidates and new lines of inquiry, illuminating the possible influence of herbal medicines on the course of cancer treatment in the future. To fully utilize herbal medicines in the battle against cancer, further research and cooperation between conventional and alternative medicine are needed, as this thorough analysis highlights.

Keywords:- Herbal Drugs, Cancer Therapy, Current Trends, Future Perspectives, Anticancer Properties, Traditional Medicine, Natural Compounds, Herbal Supplements, Clinical Trials, Bioactive Compounds, Mechanisms of Action, Safety and Efficacy, Personalized Medicine, Evidence-Based Medicine, Drug Interactions, Patient Perspectives, Regulatory Considerations, Herbal Medicine, and Quality Control.

I. INTRODUCTION

A. Cancer

The term “cancer” was used for the first time by Hippocrates, father of Western medicine, who applied the Greek words “carcinoma” and “Karakinos” to describe tumour¹. **Cancer is the uncontrolled growth of abnormal cells in the body**². Normally meiosis and cell death procedure occurs to protect the stable condition of tissues in a balanced state³. Carcinogenesis is a multistage or multi-mechanism procedure.

The initial stage of cancer includes irreversible cell changes. The promotion phase is the clonal proliferation of cells and the progression phase includes an aggressive and metastatic phase of disease. Deformed cell mass could remain inside of tissue from which it has originated and is called *in situ cancer form*. Or it can be distributed to adjacent tissues, which is called *malignant form*. More than 100 types of cancer have been recognized. Each cancer is classified according to the cell type involved at first.

According to the National Cancer Institute (NCI), classification² different types of cancer are classified as follows:

- Carcinoma
- Leukaemia
- Lymphoma and Myeloma
- Central Nerve System Cancer

According to the Global Cancer Observatory (GLOBOCAN) estimates, there were 19.3 million incident cancer cases worldwide for the year 2020⁴. India ranked third after China and the United States of America⁵. GLOBOCAN predicted that cancer cases in India would increase to 2.08 million, accounting for a rise of 57.5 percent in 2040 from 2020⁵.

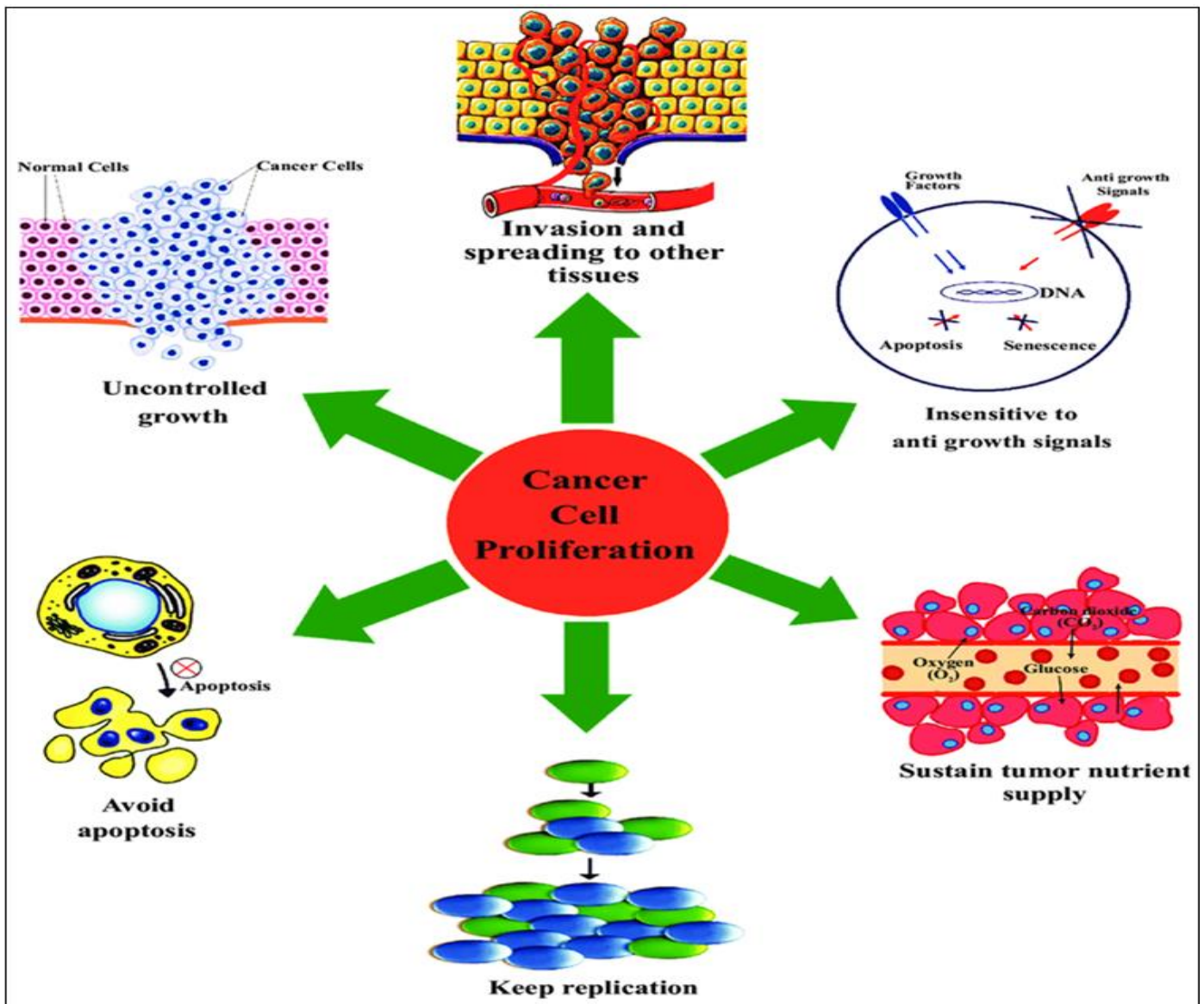


Fig 1 Proliferation of Cancer

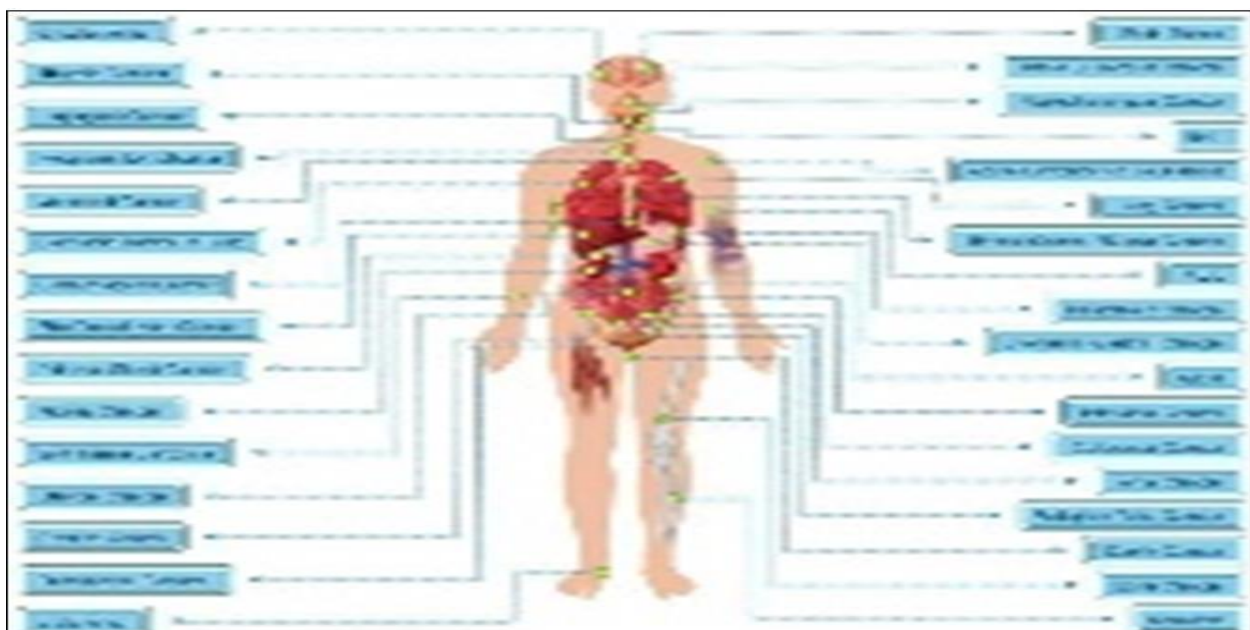


Fig 2 Types of Cancer

Surgery, chemotherapy, and radiotherapy are considered the most common methods of cancer treatment, although all of these treatment methods are not always useful and the clinical results are not acceptable⁶.

Although chemotherapy and radiotherapy are highly effective methods of cancer treatment, these methods exert severe side effects in use⁷. One of the main problems in cancer treatment is the gradual resistance of cancer cells against treatment⁸. Hence, achieving a new approach is one of the aims of immunopharmacological studies to improve cancer treatment results⁹.

From 1980 to 2000, following *Aristotle* and *Jalino's doctrine*, indicating cancer as a result of black bile coagulation, up to now during which with the advent of new treatment methods, cancer mortalities have been reduced by 25%, plants have played an important role in controlling cancer symptoms and treatments⁴.

B. Herbal Drugs

Herbal drugs include plants, herbal complexes, and herbal products or plants or even a combination of plants which were used a thousand years before inventing modern drugs. They are also used today. Herbal plants are used all over the world in different methods both in allopathic and traditional systems¹¹.

➤ Importance of Cancer Therapy

Cancer therapy is of paramount importance due to its potential to save lives and improve the quality of life for individuals diagnosed with cancer. There are several key aspects to consider when discussing the importance of cancer therapy –

- Cancer therapy, including surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapies, is often the primary or only means of treating cancer. It can help eliminate or control cancer cells, preventing the disease from spreading and becoming life-threatening¹²
- Advances in cancer therapy have led to improved survival rates for various types of cancer. Early detection and treatment can significantly increase the chances of long-term survival¹³.
- Cancer therapies are designed not only to prolong life but also to improve the quality of life for cancer patients. Palliative care, pain management, and therapies that target specific cancer cells can help reduce symptoms and side effects¹⁴.
- Cancer therapy is increasingly moving towards personalized medicine, where treatment plans are tailored to an individual's specific genetic and molecular characteristics. This approach can lead to more effective and targeted treatment¹⁵.
- Immunotherapy has emerged as a promising area in cancer treatment, harnessing the body's immune system to combat cancer. It has shown remarkable results in various types of cancer¹⁶.

- Effective cancer therapy reduces the economic burden associated with advanced cancer care, including hospitalization and supportive care costs¹⁷.

➤ Role of Herbal Drugs in Cancer Treatment

Herbal drugs, also known as botanical or plant-based medicines, have been used for centuries in traditional medicine systems for various therapeutic purposes. While they are not considered a primary cancer treatment, there is growing interest in the role of herbal drugs and their potential benefits in cancer treatment. However, it's important to note that more research is needed to fully understand their mechanisms and efficacy.

- Herbal drugs are often used in cancer care to help manage treatment-related side effects such as nausea, vomiting, fatigue, and pain.

For example; Ginger (*Zingiber officinale*) and Turmeric (*Curcuma longa*) have been studied for their potential in alleviating chemotherapy-induced nausea and vomiting^{18.1}.

- Many herbal drugs contain compounds with antioxidant and anti-inflammatory properties. Antioxidants can help protect cells from damage, which may reduce the risk of cancer.

Examples; Green Tea (*Camellia sinensis*), which contains catechins, and resveratrol found in red grapes, and *Polygonum cuspidatum* (Japanese knotweed)^{18.2}.

- Some herbal drugs have the potential to modulate the immune system, which is crucial in fighting cancer. Medicinal mushrooms like Reishi (*Ganoderma lucidum*) and Turkey tail (*Trametes versicolor*) have been investigated for their immunomodulatory effects¹⁹.
- Several herbs and plant compounds have demonstrated anti-cancer properties in preclinical studies. **For example,** compounds found in curcumin (from turmeric), epigallocatechin-3-gallate (EGCG, from green tea), and quercetin (found in various plants) have shown promise in inhibiting the growth of cancer cells and suppressing tumor development in laboratory settings²⁰.
- Herbal drugs may also play a role in cancer prevention. Some herbs and compounds, such as Garlic (*Allium sativum*), have been studied for their potential to reduce the risk of certain types of cancer²¹.

The historical use of herbal remedies in cancer therapy dates back thousands of years. Many traditional healing systems, including Ayurveda, Traditional Chinese Medicine, and Native American medicine, have employed various herbs for their potential anti-cancer properties. It's important to note that while historical practices can provide valuable insights, modern medicine relies on evidence-based cancer treatments.

Here are a few examples of historically used herbs for their use in cancer therapy:

- **Turmeric (*Curcuma longa*)**
Historical Use: Turmeric has been used in Ayurvedic medicine for centuries and is known for its anti-inflammatory and antioxidant properties. It has been suggested as a potential cancer treatment due to its active compound, curcumin²².
- **Ginseng (*Panax ginseng*)**
Historical Use: Ginseng, particularly Asian ginseng, has a long history in Traditional Chinese Medicine. It is believed to have anti-tumor and immune-enhancing properties²³.

- **Artemisinin (*Artemisia annua*)**
Historical Use: Artemisinin, derived from the sweet wormwood plant, has been used in traditional Chinese medicine for treating malaria. Research has also explored its potential in targeting cancer cells²⁴.
- **Maitake Mushroom (*Grifola frondosa*)**
Historical Use: Some studies have suggested that maitake mushrooms may have immune-boosting and anti-cancer effects²⁵.
- **Cat's Claw (*Uncaria tomentosa*)**
Historical Use: Cat's Claw, a plant native to the Amazon rainforest, has been used in traditional South American medicine. Some studies have explored its potential anti-cancer and immune-boosting properties²⁶.

Table 1 Herbal Drugs Used In Cancer Therapy Potential Advantages & Disadvantages

Herbal Drug	Advantage	Disadvantage
Astragalus (<i>Astragalus membranaceus</i>)	May boost the immune system and improve overall health.	Limited scientific evidence for its effectiveness in cancer treatment.
Echinacea (<i>Echinacea purpurea</i>)	May stimulate the immune system, helping the body fight cancer cells	Not a primary treatment and should be used in conjunction with conventional therapies.
Garlic (<i>Allium sativum</i>)	Contains organosulfur compounds that may have anticancer properties.	Its effects may vary between individuals, and it's not the sole cancer treatment.
Turmeric (<i>Curcuma longa</i>)	Contains curcumin, which has anti-inflammatory and antioxidant properties.	Not a standalone treatment, and its effects may be limited when used alone.
Mistletoe (<i>Viscum album</i>)	Some studies suggest it may enhance the quality of life and reduce side effects of cancer treatment.	Insufficient evidence to prove its effectiveness in curing cancer.
Green Tea (<i>Camellia sinensis</i>)	Contains compounds like EGCG, which have potential anticancer properties.	Limited evidence on its effectiveness, and the required dosage may be hard to achieve through tea consumption.

The use of herbal remedies in cancer treatment is a complex and often controversial subject. While some herbs and natural compounds have shown promise in laboratory studies or small clinical trials, it's essential to note that the field of herbal cancer treatment is still in its early stages. They should complement conventional treatments and not replace them.

Here are some significant milestones and notable herbal treatments associated with cancer:

- **Artemisinin (*Sweet Wormwood*):**
 Artemisinin, derived from the sweet wormwood plant, has shown potential in fighting cancer, especially in combination with conventional therapies. Research suggests it can enhance the effectiveness of chemotherapy²⁷.
- **Turmeric (*Curcuma longa*):**
 Curcumin, a compound found in turmeric, has anti-inflammatory and antioxidant properties. It is being studied for its potential in preventing and treating various types of cancer²⁸.
- **Green Tea (*EGCG*):**
 Epigallocatechin-3-gallate (EGCG), a polyphenol in green tea, has been studied for its potential to inhibit the growth of cancer cells, particularly in breast, prostate, and colon cancer²⁹.

- **Mistletoe Extract (*Iscador*):**
 Mistletoe extracts have been used in complementary cancer treatment, particularly in Europe. It's thought to stimulate the immune system and improve the quality of life for cancer patients³⁰.
- **Chinese Skullcap (*Scutellaria baicalensis*):**
 It is a Chinese herb, that contains compounds that exhibit potential anti-cancer effects, particularly in breast and prostate cancer³¹.
- **Ganoderma (*Reishi Mushroom*):**
Ganoderma lucidum, also known as reishi mushroom, is believed to have immunomodulatory effects and may be helpful in cancer prevention and treatment³².
- **Frankincense (*Boswellia serrata*):**
 Boswellic acids found in frankincense have been studied for their potential anti-inflammatory and anti-cancer properties, particularly in brain and colon cancer³³.

Table 2 Significant Milestones and Notable Herbal Treatments

Year	Milestone/Discovery	Notable Herbal Treatment
4000 BC	Early evidence of herbal remedies	Early civilizations used herbs like aloe, garlic, and myrrh.
400 BC	Hippocrates' contributions	Hippocrates described various herbal remedies for cancer symptoms.
1845	Isolation of Salicin	Salicin, found in willow bark, was the basis for aspirin, used for pain relief in cancer patients.
1960s	Vinca alkaloids	Vinca alkaloids from periwinkle plants were used in chemotherapy.
1970s	Taxol discovery	Taxol, derived from the Pacific yew tree, became a key chemotherapy drug.
1980s	Green tea extracts	EGCG in green tea showed potential as a cancer-preventive agent.
1990s	Turmeric (Curcumin)	Curcumin from turmeric demonstrated anti-cancer properties.
1996	Artemisinin and Malaria Connection	Artemisinin, an herb used for malaria, showed potential against cancer.
2000s	Cannabis and cannabinoids	Cannabinoids from cannabis gained attention for cancer symptom management.
2012	Breast cancer and black cohosh	Black cohosh was studied for its potential role in breast cancer treatment.
2019	Resveratrol research	Resveratrol from red grapes and other sources was explored for its anti-cancer effects.
2020s	Advances in herbal immunotherapy	Research continues into herbal immune-boosting remedies for cancer.

II. CURRENT TRENDS IN HERBAL CANCER THERAPY

Herbal cancer therapy, also known as phytotherapy or botanical medicine, is an area of growing interest in the field of cancer research and treatment. Many individuals are seeking complementary and alternative approaches to cancer therapy, and herbal remedies are a key component of this. However, it's important to note that herbal therapies should be used in conjunction with conventional cancer treatments and under the guidance of a qualified healthcare professional.

➤ *Here are Some Current Trends and Promising Herbal Therapies in Cancer Treatment:*

- *Curcumin from Turmeric (Curcuma longa):*

Curcumin is a bioactive compound found in turmeric, and it has shown potential for its anti-inflammatory and anticancer properties. Research suggests that curcumin can help inhibit the growth of cancer cells, reduce inflammation, and enhance the effectiveness of certain chemotherapy drugs ³⁴.

- *Green Tea (Camellia sinensis):*

Green tea contains compounds like epigallocatechin gallate (EGCG) that have been studied for their potential to inhibit the growth of cancer cells, particularly in breast, prostate, and colon cancers ³⁵.

- *Mushrooms:*

Various mushroom species, such as reishi (*Ganoderma lucidum*), maitake (*Grifola frondosa*), and turkey tail (*Trametes versicolor*), are being investigated for their immunomodulatory and anticancer properties. They may boost the immune system's response to cancer cells ³⁶.

- *Artemisinin from Sweet Wormwood (Artemisia annua):*

Artemisinin and its derivatives have been explored for their potential anticancer effects, particularly leukemia and some solid tumors. They exhibit selective toxicity towards cancer cells ³⁷.

- *Cannabis and Cannabinoids:*

Cannabis and its derivatives, including cannabidiol (CBD) and tetrahydrocannabinol (THC), have been studied for their potential in managing cancer-related symptoms, such as pain and nausea. Additionally, they may have direct antitumor effects ³⁸.

- *Indian Frankincense (Boswellia serrata):*

Boswellic acids derived from Indian frankincense have been explored for their anti-inflammatory and potential anticancer properties, particularly in brain and breast cancers ³⁹.

- *Ginger (Zingiber officinale):*

Ginger and its bioactive compounds, such as 6-gingerol, have demonstrated potential in inhibiting the growth of cancer cells and reducing inflammation ⁴⁰.

III. SUMMARY OF CLINICAL TRIALS ON HERBAL DRUGS

➤ *A variety of clinical studies have revealed that a range of anti-cancer properties from numerous herbal remedies can be explored. Globally, there are classified the clinical use of a wide variety of herbal remedies according to their suppressive impact on precise types of cancer:*

- Clinical trials have examined the anti-cancer properties of curcumin, a compound found in turmeric. Studies suggest it may help reduce inflammation and inhibit the growth of cancer cells ⁴¹.
- Epigallocatechin gallate (EGCG) from green tea has demonstrated anti-cancer potential in clinical trials. It is believed to interfere with cancer cell growth and promote apoptosis ⁴².
- Extracts from mistletoe have been tested in clinical trials, particularly in European countries, as an adjunct to cancer treatment. Some studies indicate potential benefits in terms of quality of life and survival ⁴³.

- Ganoderma extracts have shown promise in clinical trials, with potential anti-tumor and immunomodulatory effects. However, more research is needed to confirm its efficacy.⁴⁴
- Artemisinin and its derivatives have been investigated for their potential anti-cancer properties. Some studies suggest that they may selectively target cancer cells.⁴⁵

➤ *Efficacy & Safety*

- The efficacy and safety of herbal drugs used in cancer treatment can vary widely. Some herbal remedies have shown promise in preclinical studies, but clinical evidence supporting their use is often limited, and they may interact with conventional cancer treatments.
- Curcumin is a compound found in turmeric and is known for its anti-inflammatory and antioxidant properties. It has been studied for its potential anti-cancer effects⁴⁶.
- Green tea contains EGCG, a polyphenol with antioxidant properties. It has been investigated for its potential cancer prevention and treatment properties⁴⁷.
- Artemisinin is derived from the sweet wormwood plant and is mainly used as a treatment for malaria. Some research has explored its potential in cancer treatment⁴⁸.
- Maitake mushrooms contain beta-glucans and have been studied for their immune-boosting and potential anti-cancer effects⁴⁹.
- Mistletoe extract is used in complementary and alternative medicine for cancer treatment. Some studies have explored its impact on quality of life and symptom relief in cancer patients⁵⁰.

IV. MECHANISMS OF ACTION

➤ *Mechanisms by which Herbal Drugs affect Cancer Cells:*

Herbal drugs, also known as botanical medicines or phytochemicals, have been studied for their potential effects on cancer cells. The mechanisms by which herbal drugs can affect cancer cells are diverse and can involve a variety of bioactive compounds found in plants. It's important to note that while some herbal drugs have shown promise in preclinical studies or traditional medicine, their efficacy and safety in treating cancer have not been conclusively established, and further research is needed.

Here are some of the mechanisms by which herbal drugs may affect cancer cells:

• *Antioxidant Effects:*

Many herbs are rich in antioxidants, which can help neutralize harmful free radicals and reduce oxidative stress, potentially preventing DNA damage that can lead to cancer.

Examples of herbs with antioxidant properties include green tea (*Camellia sinensis*) and curcumin from turmeric (*Curcuma longa*)⁵¹.

• *Anti-Inflammatory Effects:*

Chronic inflammation is associated with the development and progression of cancer. Some herbs, such as ginger (*Zingiber officinale*) and Boswellia (*Boswellia serrata*), have anti-inflammatory properties that may help reduce inflammation in the body, potentially preventing cancer development⁵².

• *Apoptosis Induction:*

Certain herbal compounds, like resveratrol from grapes (*Vitis vinifera*) and quercetin from various sources, have been shown to induce apoptosis (programmed cell death) in cancer cells, inhibiting their growth and spread⁵³.

• *Inhibition of Angiogenesis:*

The growth of new blood vessels, a process called angiogenesis, is crucial for tumor progression. Some herbal compounds, such as epigallocatechin-3-gallate (EGCG) from green tea and genistein from soy (*Glycine max*), may inhibit angiogenesis, thus suppressing tumor growth⁵⁴.

• *Inhibition of Metastasis:*

Compounds found in herbs like curcumin and berberine may inhibit the metastasis of cancer cells, preventing them from spreading to other parts of the body⁵⁵.

• *Immune Modulation:*

Some herbs, including Astragalus (*Astragalus membranaceus*) and Echinacea (*Echinacea purpurea*), have immune-modulating properties that can enhance the body's ability to recognize and destroy cancer cells⁵⁶.

➤ *Commonly used Herbs and their Mechanisms of Action:*

Many herbs and natural compounds have been studied for their potential anti-cancer properties. It's important to note that while some studies have shown promising results, more research is needed to fully understand the mechanisms of action and their efficacy in treating or preventing cancer.

Below are some commonly used herbs and their potential anti-cancer mechanisms :

• *Curcumin (Turmeric):*

Curcumin exhibits anti-inflammatory and antioxidant properties. It can also target various signaling pathways involved in cancer development⁵⁷.

• *Green Tea (Camellia sinensis):*

Green tea contains polyphenols, such as epigallocatechin-3-gallate (EGCG), which have antioxidant and anti-inflammatory properties. They may also inhibit angiogenesis and promote apoptosis in cancer cells⁵⁸.

• *Ginger (Zingiber officinale):*

Ginger has antioxidant and anti-inflammatory effects. It may inhibit the growth of cancer cells and induce apoptosis⁵⁹.

- **Garlic (*Allium sativum*):**
Garlic contains organosulfur compounds that may have anti-cancer effects, including the inhibition of cancer cell proliferation and the induction of apoptosis⁶⁰.
- **Mushrooms (e.g., Reishi, Shiitake):**
Certain mushrooms contain compounds like polysaccharides and beta-glucans, which may stimulate the immune system and exhibit anti-cancer properties⁶¹.

- **Astragalus (*Astragalus membranaceus*):**
Astragalus has immunomodulatory effects and may enhance the body's natural defense mechanisms against cancer⁶².
- **Ashwagandha (*Withania somnifera*):**
Ashwagandha has been studied for its potential to reduce stress and inflammation, which are factors that can contribute to cancer development⁶³.

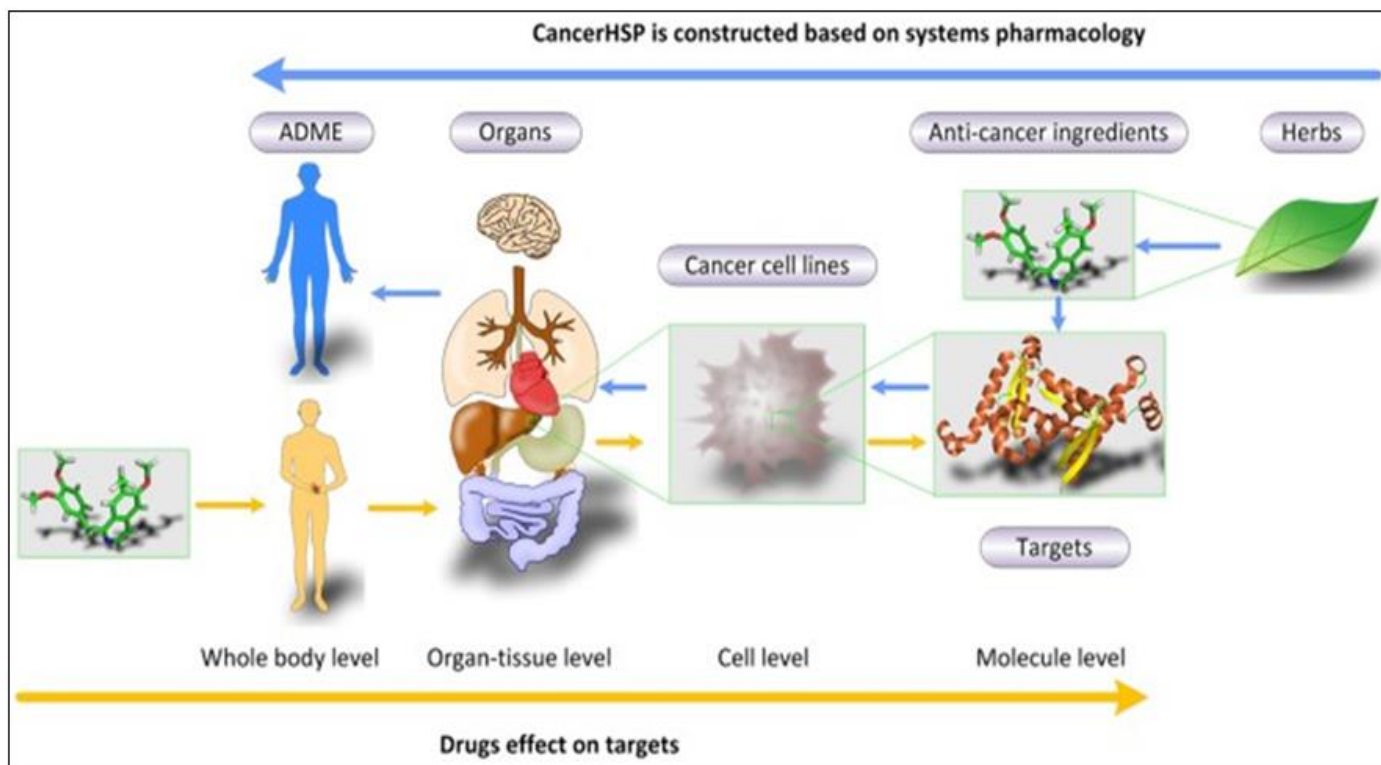


Fig 3 Mechanism of Herbal Cancer Therapy

V. CHALLENGES AND LIMITATIONS

Using herbal drugs in cancer therapy presents both potential benefits and significant challenges. While many individuals seek complementary or alternative treatments like herbal remedies for cancer, it's essential to consider the limitations and potential risks associated with this approach.

➤ Here is an overview of the challenges and limitations of using herbal drugs in cancer therapy

- **Lack of Scientific Evidence:**
One of the primary limitations of herbal drugs in cancer therapy is the lack of robust scientific evidence supporting their efficacy. Most herbal remedies lack well-designed clinical trials, and their mechanisms of action in treating cancer are often poorly understood.
- **Variability in Herbal Preparations:**
The composition and potency of herbal products can vary significantly between brands and even between batches of the same product. This lack of standardization makes it difficult to determine the proper dosing and safety of these products.

- **Interaction with Conventional Treatments:**
Herbal drugs can interact with conventional cancer treatments, such as chemotherapy and radiation therapy. These interactions may reduce the effectiveness of the treatments or lead to harmful side effects.
- **Delayed or Missed Treatment:**
Relying solely on herbal drugs for cancer treatment may lead to delayed or missed opportunities for proven and effective conventional treatments. In some cases, this can be life-threatening.
- **Potential Side Effects and Toxicity:**
Herbal remedies can have side effects and can be toxic, especially when used in high doses or for extended periods. For example, some herbs may cause liver or kidney damage, gastrointestinal issues, or allergic reactions.
- **Regulatory Issues:**
Herbal products are not as tightly regulated as pharmaceutical drugs in many countries. This can lead to concerns about product quality, safety, and accurate labeling.

- **False Hope and Financial Burden:**
Pursuing herbal treatments without evidence may give patients and their families false hope and result in significant financial burdens, as herbal products can be expensive.

- **Limited Research on Combinations:**
While there is some interest in combining herbal drugs with conventional cancer treatments, the interactions and potential synergies between these two approaches are not well understood. This lack of research can make it challenging to determine the best treatment strategies.

➤ **Issues Related to Standardization, Quality Control, and Variability**

The use of herbal drugs in cancer therapy raises several important issues related to standardization, quality control, and variability. Herbal medicines are often complex mixtures of various compounds, making it challenging to ensure their safety and efficacy.

Here are some key issues:

- **Lack of Standardization:**
Herbal products often lack standardized manufacturing processes, leading to variations in the concentration of active compounds. This can affect their therapeutic efficacy and safety⁶⁴.

- **Quality Control:**
Ensuring the quality and safety of herbal drugs is challenging due to the presence of contaminants, such as heavy metals, pesticides, and microorganisms⁶⁵.

- **Variability in Plant Sources:**
Variability in the species, plant parts, and growing conditions can lead to inconsistent herbal preparations, affecting the therapeutic outcome⁶⁶.

- **Standardization of Active Compounds:**
Herbal drugs may contain multiple active compounds, and standardizing these compounds is crucial for therapeutic consistency⁶⁷.

- **Interaction with Conventional Therapies:**
Herbal drugs used alongside conventional cancer therapies can interact with these treatments, potentially leading to adverse effects or reduced efficacy⁶⁸.

- **Lack of Clinical Evidence:**
The limited clinical evidence supporting the efficacy and safety of many herbal drugs in cancer therapy makes it difficult for healthcare providers to make informed decisions⁶⁹.

- **Regulatory Challenges:**
Regulations for herbal drugs vary widely across countries, and this lack of harmonization can impact the quality and safety of these products⁷⁰.

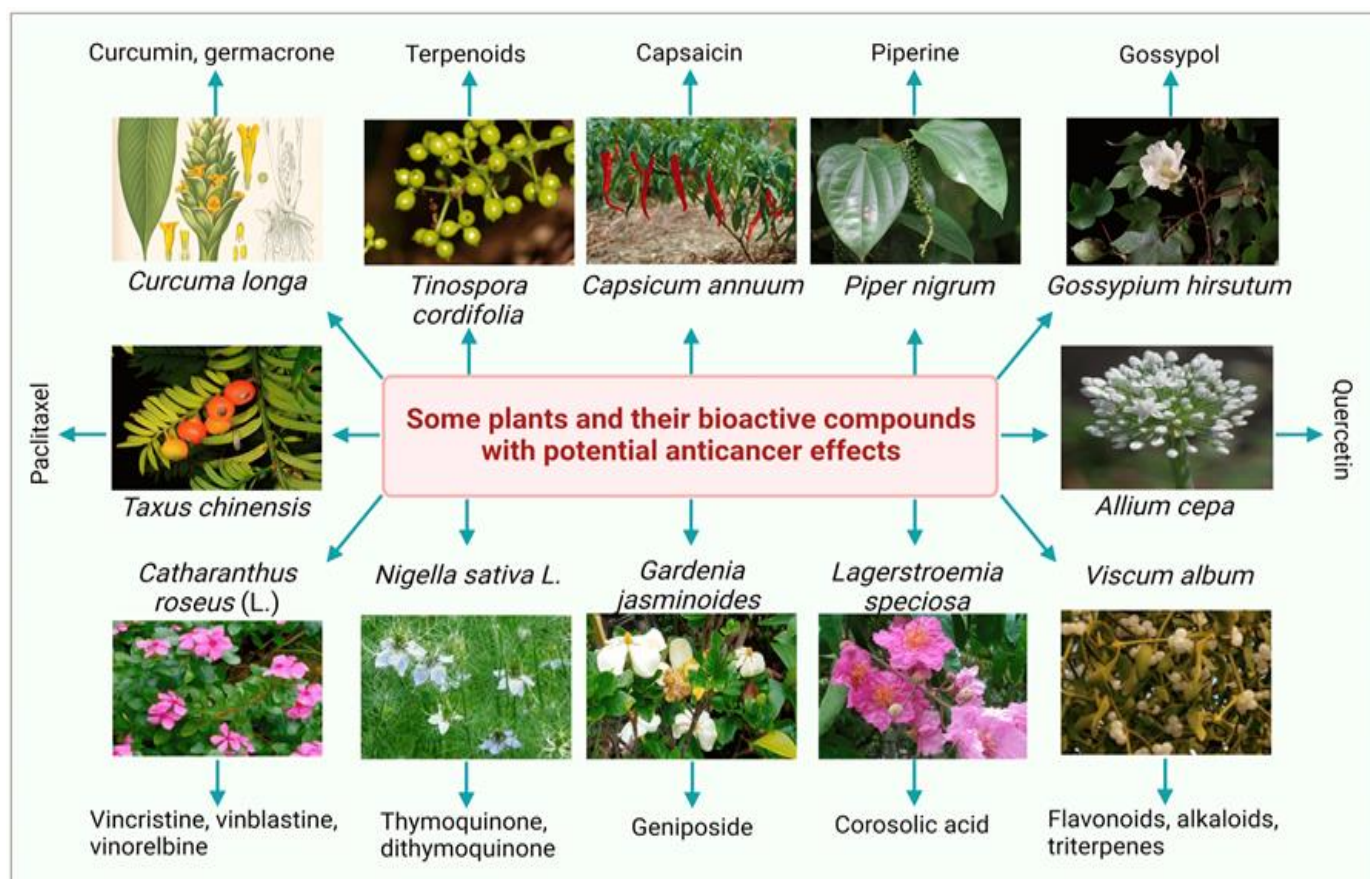


Fig 4 Plants with Bioactive Compounds of Potential Anti-Cancer Effect

VI. SYNERGY WITH CONVENTIONAL TREATMENTS

➤ *The potential of Combining Herbal Drugs with Conventional Therapies:* ^{71,72,73,74,75.}

Combining herbal drugs with conventional cancer therapies is an area of ongoing research and clinical interest. The goal is to enhance the effectiveness of cancer treatments, reduce side effects, and improve the overall quality of life for cancer patients. However, it's essential to approach this topic with caution, as herbal remedies can interact with conventional cancer treatments and may not always be safe or effective. Some herbal supplements and drugs may interfere with chemotherapy or radiation therapy. **For example, St. John's Wort**, a popular herbal remedy, can reduce the effectiveness of certain chemotherapy drugs.

Some herbal compounds have shown promise in preclinical and clinical studies for their potential anticancer properties. **For instance**, compounds found in turmeric (curcumin) and green tea (EGCG) have demonstrated anticancer effects in laboratory settings. Some herbal remedies, like echinacea, astragalus, and mistletoe extract, are believed to stimulate the immune system. This can be beneficial in cancer patients by helping the body's immune system to target and destroy cancer cells. Herbal remedies are often used to manage the side effects of cancer treatments. **For example**, ginger and peppermint can help alleviate nausea, which is a common side effect of chemotherapy.

Quality control and purity of herbal products can be a concern. It's essential to purchase herbal products from reputable sources to ensure safety and efficacy. Before using any herbal remedy in combination with conventional cancer treatments, it's crucial to consult with your oncologist or healthcare provider. They can guide potential interactions and monitor your progress. Some herbs and herbal compounds are actively being studied in clinical trials for their potential cancer-fighting properties. Participating in these trials can provide access to emerging treatments and ensure safety and efficacy.

➤ *Synergistic Effects and Improved Outcomes:*

Curcumin, a compound found in turmeric, has demonstrated anti-inflammatory and antioxidant properties. Some studies suggest that it may enhance the effectiveness of certain chemotherapy drugs, such as 5-fluorouracil and oxaliplatin. Green tea contains polyphenols, such as epigallocatechin-3-gallate (EGCG), which have been studied for their potential benefits in cancer treatment.

Some research has suggested that green tea extracts may enhance the effects of radiation therapy in certain cancer cases. Mistletoe extracts are used in anthroposophic and complementary cancer therapies. Some studies have reported an improvement in quality of life and potential immunomodulatory effects when used alongside conventional cancer treatments.

Panax ginseng, or Korean ginseng, has been studied for its potential role in alleviating cancer-related fatigue, a common side effect of cancer treatments.

VII. FUTURE PERSPECTIVES

➤ *Emerging Trends in Herbal Drug Research:*

Emerging trends in herbal drug research for cancer therapy involve the exploration of natural compounds with potential anticancer properties. While it's essential to note that herbal remedies should not replace conventional cancer treatments, they may complement existing therapies and potentially reduce side effects.

Cannabinoids derived from the Cannabis plant, particularly CBD and THC, have shown promise in preclinical and clinical studies for their potential antitumor effects. They can modulate cell proliferation, angiogenesis, and metastasis⁷⁶. Curcumin, a compound found in turmeric, has been extensively studied for its potential anticancer properties. It has demonstrated the ability to inhibit cell growth, induce apoptosis, and suppress tumor progression⁷⁷. Artemisinin, an extract from the sweet wormwood plant, has shown potential in targeting cancer stem cells. It can inhibit growth and induce apoptosis in various cancer types, making it a promising candidate in cancer therapy⁷⁸.

Resveratrol, found in grapes and red wine, has been investigated for its anticancer properties. It may modulate cell signaling pathways, induce apoptosis, and inhibit metastasis in various cancer types⁷⁹. EGCG, a polyphenol found in green tea, has demonstrated potential in inhibiting cancer cell growth, angiogenesis, and metastasis. It is being explored in various preclinical and clinical studies⁸⁰.

Various mushroom extracts, such as reishi, shiitake, and maitake, have shown immune-boosting and potential antitumor effects. They are rich in bioactive compounds like beta-glucans⁸¹. Traditional Chinese herbal medicines are increasingly studied for their potential in cancer therapy. Compounds like ginsenosides and astragalosides from ginseng and astragalus have shown promise⁸².

➤ *Direction of Future Research and Clinical Applications:*

Herbal drugs and natural compounds have shown promise in cancer therapy, and ongoing research in this field is likely to lead to new developments in the coming years.

Researchers are likely to continue identifying and characterizing bioactive compounds from various herbs, plants, and fungi with potential anti-cancer properties. These compounds could serve as the basis for new drug development. **For example**, compounds like curcumin from turmeric or resveratrol from grapes have been studied for their potential anti-cancer effects⁸³. The use of herbal drugs in combination with conventional cancer treatments such as chemotherapy or radiation therapy is an area of active research. This approach aims to enhance the effectiveness of conventional therapies while reducing their side effects⁸⁴.

Some herbal compounds have shown potential in modulating the immune system to recognize and target cancer cells. Research in this area is expected to continue with the aim of developing immunotherapies using herbal products⁸⁵. Advances in genomics and pharmacogenomics will likely play a role in tailoring herbal treatments to individual patients based on their genetic profiles. This can lead to more effective and personalized herbal therapies⁸⁶. Ensuring the safety and quality of herbal products is critical. Research on standardization, quality control, and the potential adverse effects of herbal drugs will continue to be important for their clinical application⁸⁷.

More clinical trials will be conducted to establish the safety and efficacy of herbal drugs in cancer therapy. Regulatory agencies worldwide will need to develop guidelines and regulations for herbal cancer treatments⁸⁸. Herbal drugs will continue to be explored as part of a broader approach to cancer treatment, which includes diet, exercise, and other complementary and integrative therapies⁸⁹.

VIII. SAFETY AND REGULATION

A. Regulatory Framework Surrounding Herbal Cancer Therapies:

The regulatory framework surrounding herbal cancer therapies can vary significantly by country, and it often involves a complex interplay between different regulatory agencies.

Here is a general overview of the regulatory aspects in the United States and Europe

➤ *United States:*

In the United States, the regulation of herbal cancer therapies primarily falls under the jurisdiction of the U.S. Food and Drug Administration (FDA).

The regulatory framework can be summarized as follows:

- *Dietary Supplements:*

Herbal products used for health purposes are often classified as dietary supplements. They are regulated under the *Dietary Supplement Health and Education Act (DSHEA) of 1994*. Manufacturers of dietary supplements are responsible for ensuring the safety and labeling of their products⁹⁰.

- *Health Claims:*

The FDA closely monitors health claims made by supplement manufacturers. Claims related to the prevention or treatment of cancer are subject to strict scrutiny, and manufacturers must provide substantial scientific evidence to support such claims⁹¹.

- *Good Manufacturing Practices (GMPs):*

Manufacturers of dietary supplements must adhere to GMP regulations to ensure product quality, purity, and consistency⁹².

➤ *Europe (European Union) :*

In the European Union, herbal cancer therapies are subject to comprehensive regulations, which include:

- *Traditional Herbal Medicinal Products (thumps):*

Herbal products intended for medicinal use are regulated under *Directive 2004/24/EC and the Committee on Herbal Medicinal Products (HMPC)*. To be marketed as a THMP, products must have a long history of traditional use and demonstrate their safety and efficacy⁹³.

- *Herbal Medicinal Products:*

For herbal products that do not meet the criteria for traditional use, companies may seek authorization as herbal medicinal products under the *European Medicines Agency (EMA)*. This involves rigorous scientific evaluation for safety and efficacy⁹⁴.

- *Novel Food Regulation:*

Some herbal products, especially those not commonly consumed before May 1997, may be subject to Novel Food regulations, which govern their safety and labeling⁹⁵.

B. Safety Concerns and Need for Quality Control:

Herbal drugs or botanicals have been used in traditional medicine for centuries and are often considered by some as a complementary or alternative approach to cancer therapy. However, safety concerns and the need for quality control are paramount when using herbal drugs in cancer treatment.

➤ *Here are Some Key Points:*

- *Variability in Herbal Products:*

Herbal drugs are often derived from various plant parts, and the quality and composition can vary significantly between batches and sources. This variability can affect their efficacy and safety⁹⁶.

- *Safety Concerns:*

Some herbal drugs may have adverse effects, drug interactions, or toxicity when used in cancer therapy, especially when taken concurrently with conventional treatments⁹⁷.

- *Quality Control:*

Rigorous quality control measures are essential to ensure the safety and efficacy of herbal drugs. This includes proper identification, authentication, and standardization of herbal products⁹⁸.

- *Regulatory Oversight:*

Many countries have regulatory agencies that oversee herbal products, but the level of regulation can vary. In the United States, for example, the FDA regulates herbal supplements differently from pharmaceutical drugs⁹⁹.

- *Interactions with Conventional Cancer Therapies:*

Some herbal drugs may interact with chemotherapy agents or radiation therapy, potentially reducing their effectiveness or increasing side effects¹⁰⁰.

• *Patient Education:*

Patients considering herbal drugs as part of their cancer therapy should be educated about potential risks and benefits. They should consult with healthcare professionals who know both conventional and herbal medicine¹⁰¹.

• *Research and Clinical Trials:*

Robust clinical trials and research studies are needed to assess the safety and efficacy of specific herbal drugs in cancer therapy. This can help identify which herbs may be beneficial and under what circumstances¹⁰².

IX. PERSONALIZED MEDICINE

➤ *Concept of Personalized Herbal Drugs in Cancer Therapy:*

The concept of personalized herbal drugs in cancer therapy involves tailoring herbal treatments to an individual's specific needs based on their genetic makeup, the type and stage of cancer, and other health factors. This approach is often referred to as "*precision herbal medicine*" and is gaining interest in the field of oncology. While herbal medicine has a long history of use in various traditional healing systems, the integration of personalized herbal

treatments with modern cancer therapy is a relatively new and evolving field.

Many herbal compounds have shown potential anti-cancer properties. *For instance*, curcumin from turmeric, resveratrol from grapes, and green tea polyphenols have been extensively studied for their anti-cancer effects¹⁰³. Personalized medicine in oncology involves tailoring treatments based on an individual's genetic, molecular, and clinical characteristics¹⁰⁴. Genetic and genomic information can be used to identify specific herbal remedies that might be more effective for certain individuals¹⁰⁵. Personalized herbal treatments must take into account potential interactions with conventional cancer therapies and ensure the safety of herbal remedies¹⁰⁶. Ongoing clinical trials are exploring the efficacy of personalized herbal medicine in cancer treatment. These studies provide valuable insights into the field¹⁰⁷. Different herbal compounds may be more effective for specific types of cancer. Research into these associations is crucial¹⁰⁸. Regulations and guidelines surrounding herbal remedies, especially when used in conjunction with conventional cancer treatments, must be taken into account¹⁰⁹.

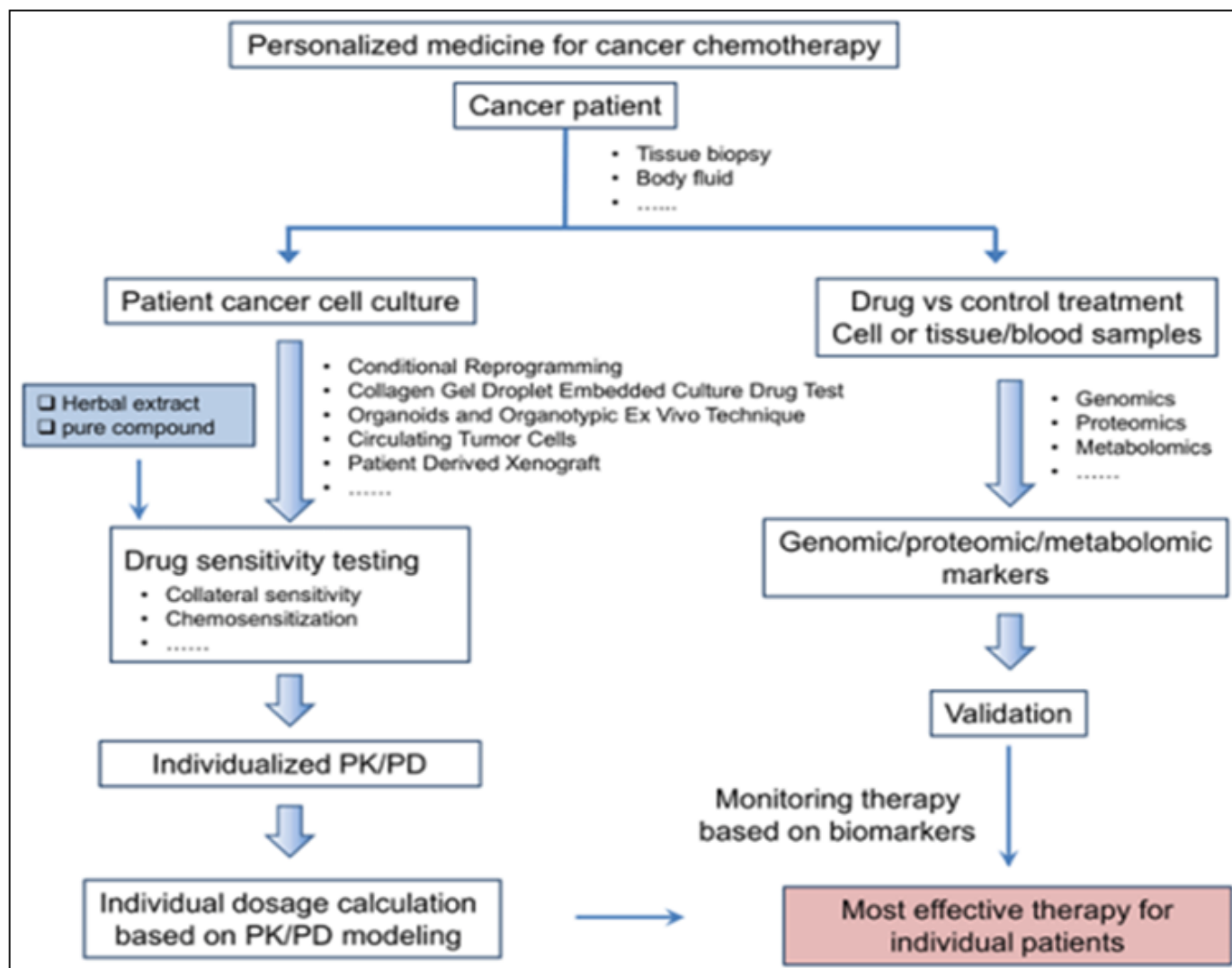


Fig 5 Personalization of Herbal Cancer Therapy

X. GENETIC PROFILING AND IMPROVED OUTCOMES

Genetic profiling and individualized approaches to herbal drugs in cancer therapy are promising strategies that can potentially improve treatment outcomes by tailoring treatments to a patient's specific genetic makeup and optimizing the use of herbal remedies.

Here's an Explanation of how this can work:

➤ *Genetic Profiling in Cancer Therapy:*

Genetic profiling, also known as molecular profiling or precision medicine, involves analyzing a patient's genetic and molecular characteristics to understand the unique genetic alterations driving their cancer. This information is crucial for selecting the most effective treatment options, including herbal remedies¹¹⁰.

➤ *Herbal Drugs in Cancer Therapy:*

Herbal drugs, or phytomedicines, have been used in various traditional medical systems for centuries. They contain bioactive compounds that can exert anti-cancer effects. However, the effectiveness of herbal remedies can vary greatly among individuals¹¹¹.

➤ *Personalized Herbal Medicine for Cancer:*

Combining genetic profiling with herbal medicine involves identifying specific genetic mutations or markers that may influence a patient's response to herbal treatments. These markers can help determine the most appropriate herbal remedies, dosages, and treatment duration for each patient¹¹².

➤ *Advantages of Individualized Herbal Cancer Therapy:*

• *Minimizing side effects:*

Tailoring herbal treatment to a patient's genetic profile can reduce the risk of adverse effects.

• *Improved efficacy:*

By targeting specific genetic markers, herbal drugs can work more effectively against the cancer's unique characteristics.

• *Personalized treatment plans:*

Patients receive treatments suited to their individual needs, enhancing overall care.

➤ *Challenges and Considerations:*

• *Regulatory hurdles:*

Integrating herbal medicine into mainstream cancer therapy requires regulatory and safety considerations.

• *Research and evidence:*

Robust clinical trials are essential to validate the efficacy and safety of herbal remedies in individualized cancer therapy.

XI. PATIENT EDUCATION AND INTEGRATION

- Patients should be well-informed about the potential benefits and risks of herbal cancer therapies so they can make educated decisions about their treatment. Without proper information, they might choose these therapies without understanding their limitations or potential interactions with conventional treatments.
- Many herbal cancer therapies may interact with prescription medications, have side effects, or interfere with ongoing treatments. Educating patients about these potential risks is crucial to their safety and overall well-being.
- Patients need to understand that the efficacy of herbal cancer therapies varies widely, and scientific evidence supporting their use is often limited. Educating patients about the available data can help manage their expectations and ensure they explore treatment options that have proven benefits.
- Integrating herbal therapies with conventional cancer treatment requires careful coordination. Patient education can help individuals understand the importance of discussing any complementary therapies with their healthcare team to ensure a holistic and safe approach to their care.
- Without proper education, patients might rely on inaccurate or misleading information from unreliable sources. Providing them with accurate and evidence-based information helps them make informed choices.
- Encouraging patients to discuss their interest in herbal therapies with their healthcare providers promotes better communication and allows the medical team to monitor and adjust treatment plans accordingly.
- Herbal cancer therapies can have side effects or adverse reactions, and patients should be aware of these possibilities to seek medical assistance promptly when necessary.
- Patients may be more likely to adhere to recommended conventional cancer treatments when they are well informed about the potential risks of solely relying on herbal therapies.
- Patients have unique medical histories, cancer types, and individual responses to treatments. Educating them about herbal therapies can lead to more personalized treatment plans that consider their specific needs and preferences.
- Patients should be informed about the importance of obtaining herbal products from reputable sources, ensuring product quality and safety.
- Herbal treatments in cancer therapy raise several ethical issues that need to be carefully considered. While many people turn to herbal remedies as complementary or alternative treatments for cancer, the use of herbs in cancer therapy should be approached with caution due to the following ethical concerns-
- Herbal treatments often lack robust scientific evidence to support their efficacy and safety in cancer therapy¹¹³.
- Patients may choose herbal treatments over conventional cancer therapies, potentially delaying effective medical interventions¹¹⁴.

- The lack of standardization in herbal products can lead to variations in the composition and potency of the remedies, raising safety concerns¹¹⁵.
- Herbal treatments may offer false hope to cancer patients and their families, leading to disappointment if they do not achieve the desired outcomes¹¹⁶.
- Herbs can interact with conventional cancer treatments, potentially reducing their effectiveness or causing adverse reactions¹¹⁷.
- Patients need to be fully informed about the potential risks and benefits of herbal treatments, and practitioners must obtain informed consent¹¹⁸.
- Some individuals and companies may exploit cancer patients' vulnerability by promoting herbal products as expensive "miracle cures"¹¹⁹.
- Consideration should be given to the cultural backgrounds and beliefs of patients when discussing herbal treatments, as cultural factors may influence their choices¹²⁰.

XII. REGULATORY FRAMEWORK

In the United States, the regulation of herbal products and dietary supplements falls under the Dietary Supplement Health and Education Act (DSHEA). The U.S. Food and Drug Administration (FDA) oversees the safety and labeling of dietary supplements¹²¹.

In the European Union, herbal products are regulated under the Traditional Herbal Medicinal Products Directive (THMPD) and may be granted a Traditional Herbal Registration¹²².

➤ *Responsible Use :*

Herbal drugs should not replace conventional cancer treatments such as chemotherapy, radiation therapy, or surgery.

➤ *Quality and Safety:*

Choose herbal products from reputable sources, as the quality and safety of herbal preparations can vary widely.

Look for Good Manufacturing Practices (GMP) certification on the product label.

Report any adverse effects or unexpected outcomes to healthcare professionals and regulatory authorities.

➤ *Informed Decision-Making:*

Patients and their healthcare providers should have open and honest discussions about the use of herbal drugs as complementary therapies.

Patients should be informed about the limited scientific evidence regarding the efficacy of herbal drugs in cancer treatment.

➤ *Research and Evidence:*

Scientific research on herbal drugs in cancer therapy is ongoing, and some herbal compounds may show promise. However, patients should be cautious and rely on evidence-based treatments¹²³.

➤ *Legal and Ethical Considerations:*

In some cases, the use of herbal drugs may be considered off-label or experimental, which should be addressed by local ethical and legal standards.

The responsible use of herbal drugs in cancer therapy requires a nuanced approach that considers individual patient needs, preferences, and clinical evidence. Patients and healthcare providers should work together to make informed decisions regarding the integration of herbal remedies into a comprehensive cancer treatment plan.

XIII. CONCLUSION

To sum up, this review has given a thorough summary of the developments that herbal medications are seeing in the field of cancer therapy, as well as their prospects. This article highlights a large body of data that shows how promising herbal medicines can be as complementary or substitutes for traditional cancer treatments. The combination of conventional knowledge with cutting-edge scientific research has a lot of potential as we traverse the complex interactions between herbal substances and their mechanisms of action.

Herbal medications have many advantages, from their low toxicity profiles to their capacity to target different cancer markers. These advantages make them an intriguing topic for further research. For these treatments to be safe and effective, however, it is crucial to stress the significance of thorough clinical studies and standardized quality control methods.

Plans for the inclusion of herbal medications in conventional cancer treatment are promising. To fully realize the benefits of herbal treatments, pharmacologists, medical professionals, and traditional healers must continue their research and work together. As we set out on our adventure, it is evident that the profound discoveries and advancements coming from the field of herbal medicine may have a substantial impact on the direction of cancer therapy.

REFERENCES

- [1]. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, et al. Natural compounds for cancer treatment and prevention. *Pharmacol Res* 2009;59(6):365-78.
- [2]. Jena J. A Study on Natural Anticancer Plants. *Int J Pharmaceut Chem Sci* 2012;1(1):365-8.
- [3]. Dhorajiya BD, Patel JR, Malani MH, Dholakiya BZ. Plant product (R)- Roscovitine valuable inhibitor of cdk5 as An anti-cancer agent. *Der Pharmacia Sinica* 2012;3(1):131-43.

- [4]. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71: 209-49.
- [5]. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: Cancer today. Lyon, France: International Agency for Research on Cancer; 2020. Available from: <https://gco.iarc.fr/today>, accessed on August 5, 2022.
- [6]. Yang G, Li X, Li X, Wang L, Li J, Song X, et al. Traditional Chinese medicine in cancer care: a review of case series published in the Chinese literature. *Evid Based Complement Alternat Med* 2012;2012:751046.
- [7]. Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, et al. Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer. *Biosci Trends* 2010;4(6):297-307.
- [8]. Wang Z, Wang N, Chen J, Shen J. Emerging glycolysis targeting and drug discovery from Chinese medicine in cancer therapy. *Evid Based Complement Alternat Med* 2012;2012:873175.
- [9]. Azadmehr A, Hajiaghaee R, Afshari A, Amirghofran Z, Refieian-Kopaei M, yousofi Darani H, et al. Evaluation of in vivo immune response activity and in vitro anti-cancer effect by *Scrophularia megalantha*. *J Med Plants Res* 2011;5(11):2365-8.
- [10]. Pal SK, Shukla Y. Herbal medicine: current status and the future. *Asian Pac J Cancer Prev* 2003;4(4):281-8.
- [11]. Smith-Hall C, Larsen HO, Pouliot M. People, plants and health: a conceptual framework for assessing changes in medicinal plant consumption. *J Ethnobiol Ethnomed* 2012;8:43.
- [12]. American Cancer Society. (2021). "Cancer Treatment & Survivorship Facts & Figures 2019-2021." <https://www.cancer.org/research/cancer-facts-statistics/survivor-facts-figures.html>
- [13]. Siegel, R. L., Miller, K. D., Jemal, A. (2020). "Cancer statistics, 2020." *CA: A Cancer Journal for Clinicians*, 70(1), 7-30. <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590>
- [14]. Temel, J. S., Greer, J. A., Muzikansky, A., et al. (2010). "Early Palliative Care for Patients with Metastatic Non–Non-Small-Cell Lung Cancer." *New England Journal of Medicine*, 363(8), 733-742. <https://www.nejm.org/doi/full/10.1056/nejmoa1000678>
- [15]. Collins, F. S., & Varmus, H. (2015). "A New Initiative on Precision Medicine." *New England Journal of Medicine*, 372(9), 793-795. <https://www.nejm.org/doi/full/10.1056/nejmp1500523>
- [16]. Hodi, F. S., O'Day, S. J., McDermott, D. F., et al. (2010). "Improved Survival with Ipilimumab in Patients with Metastatic Melanoma." *New England Journal of Medicine*, 363(8), 711-723. <https://www.nejm.org/doi/full/10.1056/nejmoa1003466>
- [17]. Sullivan, R., Peppercorn, J., Sikora, K., et al. (2011). "Delivering affordable cancer care in high-income countries." *The Lancet Oncology*, 12(10), 933-980. [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(11\)70141-3/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70141-3/fulltext)
- [18]. (18.1) Rahmani, A. H., et al. (2015). Curcumin: A Potential Candidate in Prevention of Cancer via Modulation of Molecular Pathways. *Biomed Research International*, 2014, 761608. (18.2) Rahmani, A. H., et al. (2015). Curcumin: A Potential Candidate in Prevention of Cancer via Modulation of Molecular Pathways. *Biomed Research International*, 2014, 761608.
- [19]. Yang, C. S., et al. (2010). Cancer prevention by tea: Evidence from laboratory studies. *Pharmacological Research*, 64(2), 113-122.
- [20]. Wasser, S. P. (2010). Medicinal mushroom science: History, current status, future trends, and unsolved problems. *International Journal of Medicinal Mushrooms*, 12(1), 1-16.
- [21]. Milner, J. A. (2001). Garlic: its anticarcinogenic and antitumorigenic properties. *Nutrition Reviews*, 59(3), 103-110.
- [22]. He, Z.-Y., Shi, C.-B., Wen, H., Li, F.-L., Wang, B.-L., & Wang, J. (2011). Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. *Cancer Investigation*, 29(3), 208-213.
- [23]. Yun, T. K., & Yun, Y. S. (1998). Possible anti-cancer effects of ginseng polysaccharides: An apoptin-dependent mechanism. *Biochemical Pharmacology*, 55(7), 907-914.
- [24]. Efferth, T. (2017). From ancient herb to modern drug: *Artemisia annua* and artemisinin for cancer therapy. *Seminars in Cancer Biology*, 46, 65-83.
- [25]. Vetvicka, V., Vetvickova, J., & Yvin, J. C. (2014). Antitumor effect of Pleuran (β -glucan from *Grifola frondosa*) in MOPC-315 tumor-bearing mice. *Anticancer Research*, 34(12), 7207-7210.
- [26]. Sheng, Y., Pero, R. W., Wagner, H., & Berd, D. (2000). Studies on the immunomodulating and anti-tumor activities of *Uncaria tomentosa* extract. *The Journal of Ethnopharmacology*, 73(1-2), 137-143.
- [27]. Lai, H., & Singh, N. P. (2011). Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. *Cancer Letters*, 292(1), 127-137.
- [28]. Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS Journal*, 15(1), 195-218.
- [29]. Khan, N., & Mukhtar, H. (2009). Tea polyphenols in promotion of human health. *Nutrition, Metabolism and Cardiovascular Diseases*, 19(10), 745-751.
- [30]. Ostermann, T., Raak, C., Büssing, A. (2009). Survival of cancer patients treated with mistletoe extract (Isador): a systematic literature review. *BMC Cancer*, 9, 451.
- [31]. S., & Gupta, S. (2010). Apigenin: a promising molecule for cancer prevention. *Pharmaceutical Research*, 27(6), 962-978.

- [32]. Jin, X., Ruiz Beguerie, J., Sze, D. M. Y., & Chan, G. C. F. (2016). *Ganoderma lucidum* (Reishi mushroom) for cancer treatment. *Cochrane Database of Systematic Reviews*, 4, CD007731.
- [33]. Liu, J. J., Nilsson, A., & Oredsson, S. (2010). Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent of Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis*, 31(2), 218-224.
- [34]. Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: problems and promises. *Molecular Pharmaceutics*, 4(6), 807-818.
- [35]. Khan, N., & Mukhtar, H. (2010). Tea polyphenols for health promotion. *Life Sciences*, 81(7), 519-533.
- [36]. Wasser, S. P. (2011). Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. *Applied Microbiology and Biotechnology*, 89(5), 1323-1332.
- [37]. Lai, H., & Singh, N. P. (2006). Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. *Cancer Letters*, 231(1), 43-48.
- [38]. Velasco, G., Sanchez, C., & Guzman, M. (2012). Towards the use of cannabinoids as antitumor agents. *Nature Reviews Cancer*, 12(6), 436-444.
- [39]. Liu, J. J., Nilsson, A., Oredsson, S., Badmaev, V., Zhao, W. Z., & Duan, R. D. (2002). Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent of Fas/Fas ligand interaction in colon cancer HT-29 cells. *Carcinogenesis*, 23(12), 2087-2093.
- [40]. Prasad, S., & Tyagi, A. K. (2011). Ginger and its constituents: role in prevention and treatment of gastrointestinal cancer. *Gastroenterology Research and Practice*, 2015.
- [41]. He, Z. Y., Shi, C. B., Wen, H., Li, F. L., & Wang, B. L. (2011). Antitumor effects of curcumin in human hepatocellular carcinoma: a systematic review. *Cancer Biology & Therapy*, 11(5), 480-490.
- [42]. Shi, Y., Song, Q., Hu, D., Zhuang, X., Yu, S., & Teng, D. (2017). Epigallocatechin-3-gallate (EGCG) attenuates concanavalin A-induced hepatic injury in mice. *Acta Histochemica*, 119(5), 520-526.
- [43]. Kienle, G. S., Berrino, F., Büsling, A., Portalupi, E., Rosenzweig, S., Kiene, H., & Mistletoe Study Group. (2003). Mistletoe in cancer—a systematic review on controlled clinical trials. *European Journal of Medical Research*, 8(3), 109-119.
- [44]. Gao, Y., Zhou, S., Chen, G., Jiang, W., & Huang, M. (2003). Effects of ganopoly (a *Ganoderma lucidum* polysaccharide extract) on the immune functions in advanced-stage cancer patients. *Immunological Investigations*, 32(3), 201-215.
- [45]. Lai, H., Sasaki, T., Singh, N. P., & Messay, A. (2011). Synergistic effects of artemisinin and resveratrol in cancer cells. *Anticancer Research*, 31(12), 3793-3800.
- [46]. Kunnumakkara, A. B., et al. (2017). Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *British Journal of Pharmacology*, 174(11), 1325-1348.
- [47]. Khan, N., & Mukhtar, H. (2013). Tea polyphenols for health promotion. *Life Sciences*, 93(3-4), 83-87.
- [48]. Lai, H., & Singh, N. P. (2006). Selective cancer cell cytotoxicity from exposure to dihydroartemisinin and holotransferrin. *Cancer Letters*, 231(1), 43-51.
- [49]. Vetvicka, V., et al. (2008). Glucan and cancer: comparison of commercially available β -glucans – part IV. *Anticancer Research*, 28(6A), 3629-3636.
- [50]. Kienle, G. S., & Kiene, H. (2010). Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. *European Journal of Medical Research*, 15(4), 172-183.
- [51]. Gupta, S. C., et al. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS Journal*, 15(1), 195-218.
- [52]. Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical Pharmacology*, 71(10), 1397-1421.
- [53]. Fulda, S., & Debatin, K. M. (2004). Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol. *Oncogene*, 23(40), 6702-6711.
- [54]. Gacche, R. N., & Meshram, R. J. (2013). Angiogenic factors as potential drug target: efficacy and limitations of anti-angiogenic therapy. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, 1836(2), 103-121.
- [55]. Kunnumakkara, A. B., et al. (2018). The potential of curcumin, a natural polyphenol from *Curcuma longa*, for treating human colon cancer. *Biochemical Pharmacology*, 84(6), 787-801.
- [56]. Block, K. I., et al. (2003). Immune system effects of echinacea, ginseng, and astragalus: a review. *Integrative Cancer Therapies*, 2(3), 247-267.
- [57]. Aggarwal, B. B., et al. (2013). Curcumin: The Indian Solid Gold. *Advances in Experimental Medicine and Biology*, 595-618.
- [58]. Khan, N., & Mukhtar, H. (2013). Tea Polyphenols in Promotion of Human Health. *Nutrients*, 3738-3752.
- [59]. Rastogi, N., et al. (2014). Ginger in Cancer Management: A Review. *Critical Reviews in Food Science and Nutrition*, 1-10.
- [60]. Powolny, A. A., & Singh, S. V. (2008). Multitargeted prevention and therapy of cancer by diallyl trisulfide and related *Allium* vegetable-derived organosulfur compounds. *Cancer Letters*, 8-15.
- [61]. Wasser, S. P. (2011). Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. *Applied Microbiology and Biotechnology*, 1-27.
- [62]. McCulloch, M., et al. (2006). Astragalus-Based Chinese Herbs and Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer: Meta-Analysis of Randomized Trials. *Journal of Clinical Oncology*, 419-430.
- [63]. Kataria, H., et al. (2016). Evaluation of the genotoxicity of ashwagandha. *Journal of Ethnopharmacology*, 397-404.

- [64]. De Boer, H. J., & Verpoorte, R. (2011). An approach for the identification of novel herbal mixtures by the analysis of their (1)H NMR spectra. *Phytomedicine*, 18(2-3), 293-303.
- [65]. World Health Organization. (2003). *Quality Control Methods for Medicinal Plant Materials*. Geneva.
- [66]. Rahimi, R., & Abdollahi, M. (2012). An update on the ability of St. John's wort to affect the metabolism of other drugs. *Expert Opinion on Drug Metabolism & Toxicology*, 8(6), 691-708.
- [67]. Asl, M. N., & Hosseinzadeh, H. (2008). Review of pharmacological effects of *Glycyrrhiza* sp. And its bioactive compounds. *Phytotherapy Research*, 22(6), 709-724.
- [68]. Yap, K. Y. L., & See, I. (2012). A systematic review of the incidence and prevalence of clinically significant herb-drug interactions. *Current Drug Metabolism*, 13(5), 607-647.
- [69]. Velasco, G., & Sánchez, C. (2012). Guanabenz inhibits TPA-induced colorectal cancer cell invasion and migration in vitro. *Plos ONE*, 7(8), e43369.
- [70]. WHO Traditional Medicine Strategy 2014-2023. World Health Organization.
- [71]. Yarla, N. S., et al. (2017). Curcumin: A Potent Candidate to Be Evaluated as a Potential Anticancer Drug. *The Oncologist*, 22(2), 131-149
- [72]. Conklin, K. A. (2002). Coenzyme Q10 for prevention of anthracycline-induced cardiotoxicity. *Integrative Cancer Therapies*, 1(2), 110-130
- [73]. Block, K. I., et al. (2003). Impact of antioxidant supplementation on chemotherapeutic toxicity: A systematic review of the evidence from randomized controlled trials. *International Journal of Cancer*, 103(3), 291-292
- [74]. Mcdaniel, H. R., & Complementary and Alternative Medicine in Cancer Care, I. (2009). Herbal and dietary supplements for treatment of anxiety disorders. *American Journal of Psychiatry*, 166(7), 861
- [75]. National Cancer Institute. (2020). *Complementary and Alternative Medicine for Health Professionals*. Retrieved from <https://www.cancer.gov/about-cancer/treatment/cam/hp/cam>
- [76]. Gallily, R., Yekhtin, Z., & Hanuš, L. (2015). Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacology & Pharmacy*, 6(02), 75-85
- [77]. Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS journal*, 15(1), 195-218
- [78]. Efferth, T. (2018). From ancient herb to modern drug: artemisia annua and artemisinin for cancer therapy. *Seminars in cancer biology*, 46, 65-83.]
- [79]. Cui, X., Jin, Y., Hofseth, A. B., Pena, E., Habiger, J., Chumanevich, A., ... & Hofseth, L. J. (2010). Resveratrol suppresses colitis and colon cancer associated with colitis. *Cancer prevention research*, 3(4), 549-559
- [80]. Khan, N., & Mukhtar, H. (2008). Tea polyphenols in promotion of human health. *Nutrients*, 2(9), 1231-1246.
- [81]. Guggenheim, A. G., Wright, K. M., & Zwickey, H. L. (2014). Immune modulation from five major mushrooms: application to integrative oncology. *Integrative medicine*, 13(1), 32-44.]
- [82]. Wu, Y., Zhao, Y., Li, X., & Jiang, L. L. (2016). The immunomodulating effect of ginsenosides on different Th1/Th2 cytokine profiles in mice with disseminated candidiasis. *Phytotherapy Research*, 30(6), 938-946.
- [83]. Kunnumakkara, A. B., Anand, P., & Aggarwal, B. B. (2008). Curcumin inhibits the proliferation, invasion, angiogenesis, and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Letters*, 269(2), 199-225
- [84]. Yang, Z., Zhang, Y., & Yang, H. (2020). Investigation of the combined therapeutic effect of cisplatin and quercetin on human osteosarcoma cells in vitro and in vivo. *Biological and Pharmaceutical Bulletin*, 43(7), 1141-1147
- [85]. Sengupta, S., Toh, S. A., Sellers, L. A., Skepper, J. N., Koolwijk, P., & Leung, H. W. (2002). Modulating angiogenesis: the yin and the yang in ginseng. *Circulation*, 105(5), 605-612.
- [86]. Zhou, L., Chang, D. C., & Zhan, P. (2012). Effects of apigenin on cell proliferation and NF-kappa signal transduction in U937 cells. *Molecular Medicine Reports*, 5(4), 967-971.
- [87]. De Boer, V. C., Dihal, A. A., van der Woude, H., Arts, I. C., Wolffram, S., & Alink, G. M. (2005). Tissue distribution of quercetin in rats and pigs. *The Journal of Nutrition*, 135(7), 1718-1725.
- [88]. Lawenda, B. D., Kelly, K. M., Ladas, E. J., Sagar, S. M., & Vickers, A. (2008). Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *Journal of the National Cancer Institute*, 100(11), 773-783.
- [89]. Greenlee, H., Dupont-Reyes, M. J., Balneaves, L. G., Carlson, L. E., Cohen, M. R., Deng, G., ... & Zick, S. M. (2017). Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA: A Cancer Journal for Clinicians*, 67(3), 194-232.
- [90]. U.S. Food and Drug Administration. (2021). [Dietary Supplements](<https://www.fda.gov/food/dietary-supplements>).
- [91]. U.S. Food and Drug Administration. (2019). [Structure/Function Claims](<https://www.fda.gov/food/cfsan-constituent-updates/fda-reiterates-its-concerns-about-health-claims-cbd-and-stresses-it-may-consider-regulation>).
- [92]. U.S. Food and Drug Administration. (2007). [Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements](<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/dietary-supplement-current-good-manufacturing-practice-cgmp-final-rule>).

- [93]. European Medicines Agency. (2021). [Committee on Herbal Medicinal Products (HMPC)] (<https://www.ema.europa.eu/en/committees/committee-herbal-medicinal-products-hmpc>).
- [94]. European Medicines Agency. (2021). [Herbal Medicinal Products](<https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products>).
- [95]. European Commission. (2018). [Novel Food](https://ec.europa.eu/food/safety/novel-food_en).
- [96]. De Smet, P. A. (2002). The role of plant-derived drugs and herbal medicines in healthcare. *Drugs*, 62(2), 195-232.
- [97]. Ernst, E. (2002). The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Annals of Internal Medicine*, 136(1), 42-53.
- [98]. Heinrich, M., Barnes, J., Gibbons, S., & Williamson, E. M. (2012). *Fundamentals of Pharmacognosy and Phytotherapy*. Churchill Livingstone.
- [99]. Dietary Supplement Health and Education Act of 1994. Public Law 103-417, 103rd Congress.
- [100]. Sparreboom, A., Cox, M. C., & Acharya, M. R. (2004). Herbal remedies in the United States: potential adverse interactions with anticancer agents. *Journal of Clinical Oncology*, 22(12), 2489-2503.
- [101]. Block, K. I., Gyllenhaal, C., Lowe, L., & Amedei, A. (2015). Designing a broad-spectrum integrative approach for cancer prevention and treatment. *Seminars in Cancer Biology*, 35, S276-S304.
- [102]. Ben-Arye, E., Samuels, N., & Lavie, O. (2019). Incorporating Complementary Medicine in Supportive Cancer Care Models: What Do Oncologists Need for Safe, Informed Decision-Making? *Integrative Cancer Therapies*, 18, 1534735419831001.
- [103]. Saif, M. W., Lansigan, F., & Ruta, S. (2010). Herbal products are a class of dietary supplements with anti-tumor effects: Current challenges in cancer care. *The American Journal of Blood Research*, 1(2), 102-114.
- [104]. Garraway, L. A., & Lander, E. S. (2013). Lessons from the cancer genome. *Cell*, 153(1), 17-37.
- [105]. Henn, B. M., & Cavalli-Sforza, L. L. (2012). Genomics and the origin of species. *Nature Reviews Genetics*, 13(2), 161-171.
- [106]. Izzo, A. A., & Ernst, E. (2009). Interactions between herbal medicines and prescribed drugs: A systematic review. *Drugs*, 69(13), 1777-1798.
- [107]. National Cancer Institute (NCI). (2023). *Complementary and Alternative Medicine in Cancer Treatment*. [<https://www.cancer.gov/about-cancer/treatment/cam>]
- [108]. Yarla, N. S., et al. (2017). Targeting the diverse landscape of the immune system with the potential use of herbal medicine: A promising approach for the treatment of cancer and inflammation. *Omics: A Journal of Integrative Biology*, 21(7), 393-404.
- [109]. World Health Organization (WHO). (2005). *National policy on traditional medicine and regulation of herbal medicines: Report of a WHO global survey*.
- [110]. Schwaederle, M., Zhao, M., Lee, J.J., et al. (2015). Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *JCO Precision Oncology*, 1, 1-16. Doi: 10.1200/PO.15.00042
- [111]. Han, H.K., Lee, W.S. (2020). Nanoparticle-Mediated Co-Delivery of Chemotherapeutic Agent and Sirna for Combination Cancer Therapy. *Expert Opinion on Drug Delivery*, 17(2), 1-21. Doi: 10.1080/17425247.2019.1707636
- [112]. Yarla, N.S., Bishayee, A., Sethi, G., et al. (2017). Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. *Seminars in Cancer Biology*, 40-41, 48-81. Doi: 10.1016/j.semcancer.2016.09.003
- [113]. Milazzo, S., et al. (2013). Quality of life in patients with colorectal cancer receiving adjuvant chemotherapy: a systematic review. *European Journal of Cancer Care*, 22(6), 750-761.
- [114]. Cassileth, B. R., & Vickers, A. J. (2005). High prevalence of complementary and alternative medicine use among cancer patients: implications for research and clinical care. *Journal of Clinical Oncology*, 23(12), 2590-2592.
- [115]. Ernst, E. (2002). Toxic heavy metals and undeclared drugs in Asian herbal medicines. *Trends in Pharmacological Sciences*, 23(3), 136-139.
- [116]. Johnson, S. B., & Park, H. S. (2017). The potential for false hope: unproven cancer drugs and the risk of patient suicide. *Bioethics*, 31(8), 600-606.
- [117]. Sparreboom, A., et al. (2004). Herbal supplements—Drug interactions: scientific and regulatory perspectives. *Clinical Pharmacology & Therapeutics*, 75(1), 2-6.
- [118]. Lee, R. T., & Barbo, A. (2017). Ethical issues in complementary and alternative medicine. In *Complementary and Alternative Medicine for Older Adults* (pp. 109-119). Springer.
- [119]. Johnson, S. B., & Park, H. S. (2015). Exploiting hope: promoting unproven stem cell therapies. *Journal of Law, Medicine & Ethics*, 43(1), 143-154.
- [120]. Lee, R. T., & Barbo, A. (2017). Cultural competence in complementary and alternative medicine. In *Complementary and Alternative Medicine for Older Adults* (pp. 121-131). Springer.
- [121]. U.S. FDA - Dietary Supplements: <https://www.fda.gov/food/dietary-supplements>
- [122]. European Medicines Agency (EMA) - Herbal Medicinal Products: <https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products>
- [123]. National Cancer Institute (NCI) - Complementary and Alternative Medicine for Cancer: <https://www.cancer.gov/about-cancer/treatment/cam>.