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Review Article

Navigating Apoptosis: Exploring The Potential Of Herbal Medicine As Caspase Inducers In Cancer Therapy

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ABSTRACT

The principal aim of this review is to systematically aggregate comprehensive data pertaining to herbal drugs employed in the therapeutic intervention of cancer, with a specific emphasis on the caspase-dependent apoptotic pathway. The primary focus encompasses the meticulous compilation of information encompassing various herbal drugs, elucidating details such as the specific botanical source, the targeted caspase mode of action, and the associated types of cancer. By synthesizing this information, the review aims to furnish an enhanced comprehension of the utility of herbal drugs in relation to conventional chemotherapeutic modalities, thereby contributing to a more nuanced understanding of their therapeutic potential in cancer treatment.

INTRODUCTION

Global burden of cancer

Around the world, about 19.3 million people are diagnosed with cancer. The global incidence of cancer is expected to rise to 28.4 million by 2040, marking a 47% increase compared to 2020. The rise is expected to be more significant in countries that are transitioning (from 64% to 95%) compared to those that have already transitioned (from 32% to 56%). This increase is mainly due to changes in population, and it might be made worse by factors linked to globalization and economic growth. It's crucial to work on creating a reliable system to spread cancer prevention methods and provide cancer care in transitioning countries to effectively control cancer worldwide [1]

In 2022, it was estimated that around 14,61,427 people in India would be diagnosed with cancer, with a rate of 100.4 cases per 100,000 people. This means about one in nine individuals in India might get cancer during their life. The most common types of cancer in men and women were lung and breast cancers, respectively. For children aged 0-14 years, lymphoid leukemia was the most prevalent type. It's anticipated that the number of

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cancer cases will go up by 12.8% in 2025 compared to 2020[2]

On December 14th, IARC shared new information about the global cancer situation. The latest update, called Globocan 2020, shows that 2020, there were 19.3 million cancer cases and 10 million deaths attributed to cancer globally [3]

Limitations of conventional treatment

One big problem with usual treatments is that they aren't very specific. Take chemotherapy, for example. It goes after cells that divide quickly, but it doesn't distinguish between cancer cells and healthy ones. This lack of selectivity is why patients often suffer from severe side effects during these treatments [4]

Cancer cells can change and resist chemotherapy or radiation, making the treatment not work well, and the disease can come back. The reasons for this resistance are complicated and involve things like genetic changes, different pathways in the body, and special cancer cells called stem cells.[5]

Regular treatments have improved, but they might not always completely get rid of cancer cells, especially when it spreads. Some cancer cells can stick around even after strong treatments, causing the cancer to come back and requiring more interventions [6]

Apoptosis and cancer

Apoptosis pathway

The nomenclature "apoptosis" is introduced to designate a previously underappreciated mechanism of regulated cellular deletion. This mechanism is observed to function as a complementary, albeit opposing, counterpart to mitosis in the orchestration of animal cell populations.[12] Apoptosis, a conserved process, entails distinct morphological changes like chromatin condensation and nuclear fragmentation [13]. Cellular rounding, reduced volume, and pseudopod retraction occur.[12] The plasma membrane remains intact initially, progressing to membrane blebbing and organelle changes. Phagocytosis often prevents apoptotic bodies. Failure leads to secondary necrosis, resembling necrosis. [14]

Apoptosis is a physiological phenomenon inherent in developmental processes and aging, serving as a homeostatic mechanism crucial for the regulation of cellular Populations within tissues. Moreover, apoptosis acts as a protective mechanism, especially during immune responses or when cellular damage occurs due to pathological conditions or harmful agents. [15]

The role of caspases in apoptosis

Apoptosis is a highly complex process involving an energy-dependent series of molecular events. [16,17].

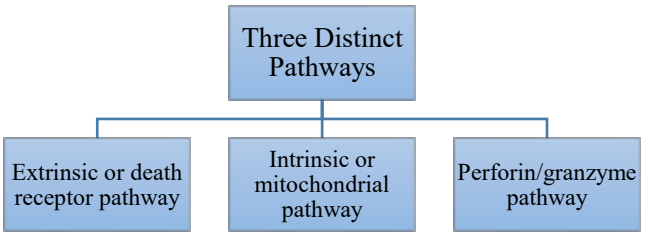

Figure 1: Apoptotic Pathways

The initiation of apoptosis through extrinsic signaling pathways involves interactions mediated by transmembrane receptors. Specifically, death receptors, which belong to the tumor necrosis factor (TNF) receptor superfamily, play a crucial role in this process.[18] Positive stimuli like radiation, toxins, hypoxia, hyperthermia, viral infections, and free radicals cause changes in the inner mitochondrial membrane. This triggers the opening of the mitochondrial permeability transition (MPT) pore, leading to the loss of mitochondrial transmembrane potential. Consequently, pro-apoptotic proteins are released from the intermembrane space into the cytosol. [19]

T-cell mediated cytotoxicity, a form of type IV hypersensitivity, involves sensitized $CD8^+$ T cells targeting and eliminating cells that present specific antigens. Cytotoxic T lymphocytes (CTLs) execute cell death primarily via the extrinsic pathway, with the interaction between Fas ligand

(FasL) on the CTLs and Fas receptor (FasR) on the target cells being the main mechanism driving CTL-induced apoptosis. [20]

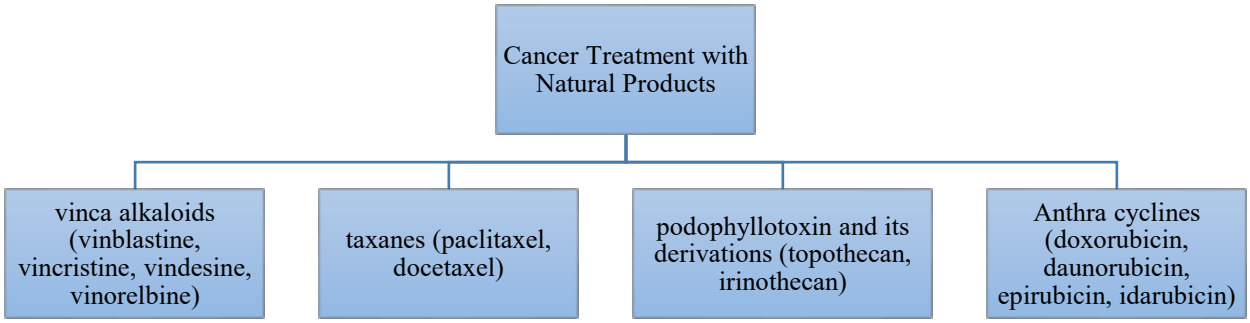

Figure 2: Different Natural Products used in Treatment of Cancer

These findings led to the identification of novel chemotypes exhibiting cytotoxic activities, such as taxanes and camptothecins. The development of these drugs took approximately three decades (1960-1990) before they were incorporated into clinical practice [11]

Implications for cancer therapy:

Upon apoptosis initiation, intracellular modifications ensue, marked by caspase activation. Caspases cleave vital cellular elements like cytoskeletal and nuclear proteins, disrupting normal cellular function. This enzymatic activity induces apoptotic cell contraction and triggers alterations in the plasma membrane, serving as signals for macrophage response [21] Apoptosis is executed by caspases, a class of cysteine proteases specifically targeting and cleaving proteins.[22] Caspase protease activity is essential for effective apoptosis, as these enzymes cleave hundreds of different proteins [23][22]

Table 1: Caspases and their Role [22]

Caspase Type	***Caspases***	***Roles in Apoptosis***
Initiator	Caspase-2, Caspase-8,	Initiate the apoptosis signaling cascade by
	Caspase-9, Caspase-10	activating downstream caspases and signaling
Executioner	Caspase-3, Caspase-6,	Execute the apoptotic process by cleaving
	Caspase-7	specific cellular proteins and causing cell death

The universal characteristics of cancer, found in all cancer cells irrespective of their origin or type, encompass unbridled proliferation, angiogenesis, and resistance to apoptosis [24,25]

Treating cancer involves controlling cell growth, often by utilizing the cell's programmed death mechanism, apoptosis. Targeting apoptosis is a successful non-surgical approach effective across various cancer types. Many anticancer drugs focus on different stages in intrinsic and extrinsic apoptotic pathways [26,27,28]

Rationale for focusing on herbal drugs:

Herbal drugs, made from plants or combinations of plants, have been in use for thousands of years, predating modern pharmaceuticals. Today, these natural remedies remain relevant and are still employed as alternative or complementary treatments.[7] With the onset of the industrial revolution and the introduction of contemporary pharmaceuticals, the utilization of herbal plants underwent a temporary cessation [7] However, impediments to the investigation of natural compounds have recently diminished predominantly through the application of modern techniques.[8] This has led to more interest in using

natural substances in making medicines [9] Out of 121 drugs prescribed for cancer treatment, 90 originate from herbal medicine. According to a study, among the 65 newly registered drugs for cancer treatment between 1981 and 2002, 48 were derived from natural products [10]

Natural and herbal drugs overview:

Importance of natural and herbal drugs.

Natural compounds derived from plants, microorganisms, and marine life exhibit strong anticancer properties by triggering cell death through diverse pathways such as apoptosis, autophagy, necroptosis, paraptosis, parthanatos, or mitotic catastrophe. These effects entail complex molecular mechanisms, including epigenetic regulation, protein kinase cascades, and nuclear/mitochondrial processes, as extensively discussed in the literature. [29,30-35,36-43]

Historical context of herbal medicine in cancer treatment:

Traditional Chinese Medicine (TCM), practiced for centuries, is widely acknowledged as an alternative cancer treatment. It outlines TCM's molecular mechanisms, emphasizing phytochemicals (curcumin, resveratrol, berberine), the role of oncogenes and tumor suppressor genes, epigenetic influences (DNA methylation, histone modification, noncoding RNAs), and TCM's impact on the tumor microenvironment and cancer stem cells. The comprehensive information provided serves as a foundational resource for future research in TCM-based cancer therapy [87]

Table 2: In-depth Discussion of Specific Herbal Compounds known for Inducing Caspases

Sr. No.	Plant Name	Part of Plant Used	Phytoconstituent	Type of Caspase Targeted	Type of Cancer Targeting	Other Benefits	References
1	Croton Tiglium	Seed	Tetradecanoylphorbol-13-acetate	Caspase-3	Breast cancer	Constipation, abdominal pain, peptic ulcer and intestinal inflammation	44, 45
2	Euphorbia Royleana	Aerial parts (stem bark)	Phenols, flavonoids, and steroids	Caspases 9	Breast cancer	Paralysis, ear pain, and diarrhea, as well as anti-inflammatory and anti-arthritic properties	44, 45
3	Achillea Fragrantissima	Flower,leaves, root	Flavanoids, alkaloids, Polyacetylenes essential oils	Caspases-3/7	Breast cancer	Diabetes, respiratory disorders, gastrointestinal disturbances, dysmenorrhea, eye infections, smallpox, fever, headaches, and fatigue	46, 47
4	St. John's wort	Flower	Hypericin	Caspases 9, 8, and 3	Thyroid cancer	Anti-depressive, anti-neoplastic, anti-angiogenic, and anti-viral properties	48
5	Artemisia absinthium	Leaves	Costunolide, thujone, and artemisinin	Caspase 3/9	Breast, lung cancer	Alleviate pain and swelling, and to treat digestive issues, intestinal worms, and skin infections	49, 50
6	Rhinacanthus nasutus	Roots	Rhinacanthin-C	Caspase 3	Oral cancer cells	Skin infections, diabetes,	51

						inflammatory disorders	
7	Garcinia hanburyi	Bark	Gambogic acid	Caspase-3.	Colorectal cancer cells	Constipation	52
8	Hypericum roeperianum	Bark	Fridelan-3-one, betulinic acid	Caspase-9	Breast cancer	Female sterility, fungal infections	53, 54]
9	Euphorbia granulata	Leaves	Rutin	Caspase 3	Breast cancer cells	Antioxidant, antibacterial, antifungal, diuretic, anti-ulcerative colitis and spasmolytic properties	55, 56
10	Caesalpinia sappan L.	Stem	Sappanchalcone	Caspase-9	Colon cancer	Antioxidant, anti-inflammatory properties, diarrhea, diabetes, and blood stasis	57
11	Moutan Cortex Radicis	Root bark	Paeoniaceae	Caspases 3, 8 and 9	Gastric cancer cells	Eliminating heat, promoting blood flow, removing blood stasis, anti-oxidant, hepatoprotective, neuro-protective	58
12	Streptococcus agalactiae	Gram positive coccus	Fusion protein	Caspase-3	Cervical cancer cells	Vaccine development, Probiotics	59
13	Ganoderma lucidum	Sporoderm-broken spores	Polysaccharide	Caspase-3 and 9	Breast cancer cells	Antineoplastic, free radical scavenger, antibacterial	60, 61
14	Ginger	Rhizome	Ginger polysaccharide UGP1	Caspase-3	Human colon cancer	Nausea and vomiting, menstrual cramps, osteoarthritis, diabetes, migraine headaches	62
15	Corchorus olitorius	Leaves	Phenols and flavanoids	Caspase-3,	Breast and lung cancer cell lines	Fever, chronic cystitis, cold and tumours.	63
16	Dracocephalum palmatum Stephan	Dried leaves	phenols and flavanoids	Caspase-8	Human prostate cancer	Anti-oxidant	64
17	Hedychium spicatum	Rhizome	β-pinene, eucalyptol, sabinene, trans-isolimonene	Caspases 3, 8 and 9	Human prostate adenocarcina	Inflammation, pain, asthma, halitosis, vomiting, diarrhea, bronchitis, hiccups, and blood disorders.	65, 66
18	Rhinella marina	Parotoids macroglandules	Marinobufotoxin	Caspases 3 and 9	Human breast and ovarian cancer cells	Anti-inflammatory	67, 68
19	Anacyclus pyrethrum	Leaves and stems	Alkylamides	Caspases 3, 8 and 9	Lung cancer cell line	Antimicrobial, anti-inflammatory, antidiabetic, insecticidal, immunostimulatory, aphrodisiac, antioxidant	69, 70

20	Huang qin	Roots	Baicalin	Caspase-3 and 9	Gastric cancer cells	Fevers, gastrointestinal issues, and liver disease	71, 72
21	Vateria indica	Leaves	Cladosporium oxysporum	caspases 3 and 8	colon cancer cell line	chronic bronchitis, throat ailments, cough, asthma, leprosy, skin eruptions, fungal infections, wounds, and ulcers.	73
22	Angelica sinensis	fresh roots	Angelica sinensis polysaccharide	caspase-3	human breast cancer cells	a tonic, hematopoietic, and anti-inflammatory agent used in the treatment of menstrual irregularities, dysmenorrhea, and amenorrhea.	74
23	Manilkara zapota	Leaves	--	Caspases 3 and 8	Human colorectal cancer cell line	Diarrhea and pulmonary infections, cough, cold,	75
24	Genus Gossypium	Seeds, roots, and stems	Gossypol	Caspases 3	Human prostate cancer cells	Male contraceptive, HIV/AID	76
25	Azadirachta indica	Leaves	Azadirachtin	Caspases 3 and 8	Cancer cells	Anti-inflammatory, anti-arthritic, antipyretic, hypoglycemic, anti-gastric ulcer, antifungal, antibacterial, and anti-tumor properties	77, 78, 79, 80
26	Camellia sinensis	Buds and young leaves	Flavanoids and phenols	Caspase-3/7, -8 and -9	Colon cancer cell line	antioxidant, antiviral, anticancer, antibacterial, antifungal, antitoxoplasmal, antitrypanosomal, anticoccidial, antinematodal and antihelminthic	81, 82
27	Olea europaea L. cv. Chetoui	Leaf and stem	Oleuropein	Caspase 3/7	Human multiple myeloma cells	Diabetes, hypertension, inflammation, diarrhea, respiratory and urinary tract infections, gastrointestinal disorders, asthma, hemorrhoids, rheumatism, as a laxative, mouth cleanser, and as a vasodilator.	83, 84

28	Cassia auriculata Linn.	Aerial parts	Flavone, chrysin, and quercetin.	Caspase 9	Lung cancer cell lines	Diabetes, pink eye, joint and muscle pain (rheumatism), constipation	85
29	Wild pink bayberry	Fruit	Gallic acid, Myricetin	Caspase-3	Cancer cells	Colds, diarrhea, nausea, skin wounds	86

Mechanism of action:

Medications used in cancer treatment often trigger signaling pathways that lead to the activation of caspases, a group of cysteine proteases pivotal in numerous cell death processes [88]

1) Exploration of the mechanisms through which natural compounds induce caspases:

Caspases can be activated through two main mechanisms. In the induced proximity model, initiator caspases like caspase-8 or caspase-9 are activated within distinct complexes, such as caspase-8 within the death-inducing signaling complex (DISC) and caspase-9 within the apoptosome [89-93]

In an alternative pathway, caspases can be activated by undergoing enzymatic processing of their inactive forms at specific cleavage sites. [90]

Activation of caspases can originate from various sources, such as signaling at the cellular membrane through death receptors (receptor pathway) or from within the mitochondria (mitochondrial pathway) [89,90]

Activation of death receptors from the tumor necrosis factor (TNF) receptor superfamily, such as CD95 (APO-1/Fas) or TRAIL receptors, leads to receptor clustering and the recruitment of the adaptor protein Fas-associated death domain (FADD) along with caspase-8 [91-93]

2) Regulation of caspase activation:

Caspases play a crucial role in drug-induced apoptosis, influencing sensitivity or resistance to cancer treatments. Surprisingly, tumors show low caspase mutations, but rather, epigenetic downregulation, emphasizing the potential of restoring functional caspase systems to overcome resistance [94-96]

3) Caspase expression:

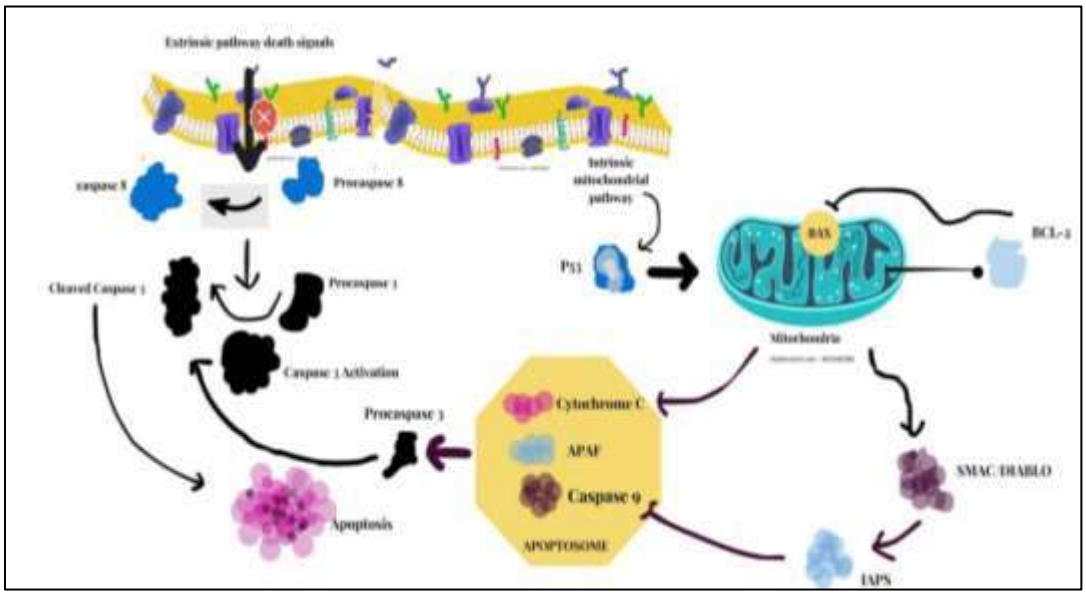

Figure 3: Caspase Expression

Synergistic effects or interactions with conventional cancer treatments

Recent advancements in combined chemotherapy, involving multiple drugs targeting diverse

biochemical and molecular pathways, enhance efficacy while minimizing adverse effects [97,98]

Experimental findings provide evidence for the synergistic impact of natural compounds in conjunction with chemotherapy, demonstrating the potential of combining antitumoral agents with various natural compounds to augment efficacy in cancer therapy.

Table 3: Synergistic Effects of Herbal Compounds with Conventional Cancer Treatments

Sr. No.	Natural compounds	Antineoplastic agents	Reference
1.	Curcumin	5-fluorouracil	99
2.	Curcumin	Cisplatin	100
3	Resveratrol	5-fluorouracil	101
4	Caffeic acid	Cisplatin	102
5	Luteolin	Cisplatin	103
6	Epigallocatechin-3-gallate	Doxorubicin	104
7	Urolithin A	Oxaliplatin	105

Safety and Side Effects:

Herbal medicines, while potentially causing fewer side effects compared to conventional drugs, can still lead to complications. Negative interactions with chemotherapy drugs or impaired blood clotting post-surgery are possible issues associated with certain herbs [106]

Although commonly viewed as safe because of their natural origins, herbal medicines can produce adverse effects, varying from mild to severe, including allergic reactions, asthma, headaches, nausea, vomiting, and diarrhea. It's important to recognize that, similar to conventional prescription drugs, herbal medicines should be administered by qualified and licensed practitioners. Seeking guidance from professional organizations affiliated with the specific therapy is recommended to access a roster of certified practitioners in your locality [107]

Conclusion and Future Directions:

Given that nearly 50% of existing pharmaceuticals have plant origins, exploring natural sources, particularly plants, for effective cancer treatment is evident. Historically, deriving Medications derived from natural sources, such as botanicals, was a time-consuming process. However, modern techniques have significantly expedited the discovery of active plant compounds, leading to a resurgence in the use of herbal plants. The revitalization of medications sourced from herbs, particularly in the treatment of cancer, immunological, and central nervous system (CNS) disorders, holds great importance. Presently, more than 60 herbal complexes are under investigation for their potential as anti-cancer agents. Despite this progress, the efficacy and safety of herbal products remain insufficiently understood. Neglecting the common usage of such products underscores the need for further research to enhance the appropriate utilization of plant-derived products. This is particularly crucial in addressing the gaps in knowledge regarding the effectiveness and safety of herbal interventions.

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