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An Extensive Review on Medicinal Plants, Polyherbal Formulations, and Phytoactive Constituents Against Squamous Cell Carcinoma

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Abstract: Cancer is a dreadful disease worldwide that affects all the organs of the human body. Squamous cell carcinoma is a solid tumor that occurs in the squamous epithelia of many organs, resulting in the death of many people due to the high rate of metastasis. The common treatment methods result in severe side effects. Hence, alternative therapy is in demand. Medicinal plants and their active metabolites have been used for the treatment of numerous diseases for many decades with minimal side effects. Polyherbal medicine has been used for many years and is simpler than a single herb due to its synergistic effects and fewer side effects. This critical review is on the formulation of herbal and polyherbal combinations for the treatment of squamous cell carcinoma. This review is based on a thorough evaluation of the literature, undertaken using Web of Science, Scopus, PubMed, and Google Scholar to search for pertinent keywords. An in-depth study of the research studies found in this review indicates that polyherbal formulations and herbs are significant in the defense against various types of squamous cell carcinoma at various sites. The results of the *in vitro* investigations demonstrated that secondary metabolites present in plant extracts inhibit neoplastic cells by inducing cell cycle arrest, promoting apoptosis, and altering signal transduction. Preparation and production of a standard herbal medication for cancer treatment require additional research on polyherbal formulations, phytoactive ingredients, and the mechanisms behind their anticancer effects.

Keywords: cancer; squamous carcinoma; phytocompounds; polyherbal formulation; anticancer activity; medicinal plants.

1. Introduction

Cancer is a widespread disease that affects both developed and emerging nations and results from unregulated cell growth. GLOBOCAN 2022 anticipated 20 million new cases, of which 14,13,316 instances were recorded in India, with the major cancers being breast, lip, oral cavity, and cervix uteri [1]. In 80–90% of all cancer cases, epithelial tissue cancers known as carcinomas are the most common type, which can develop in a variety of body parts. The most frequent solid tumors in humans are squamous cell carcinomas (SCCs) [2].

Cancer can be detected using biomarkers, and treatment can be based on that. Chemotherapy, hormone therapy, immunotherapy, photodynamic therapy, radiation, stem cell transplant, surgery, and targeted therapy are some of the most common treatment options, according to the National Cancer Institute. These treatments are effective but have various side effects, and they vary from person to person [3].

Since ancient times, people have used plants and products derived from them to treat illnesses and as preventive medicine. The plant-based products and their detailed therapeutic effects are well explained in Charaka Samhita, Sushruta Samhita, Ashtangahrida Samhita, and Bhavaprakasha Nighantu [4]. More than 60% of the medications used to treat different cancers are derived from plants, either in their raw or isolated phyto-molecular form. Due to their synergistic impact, the medicinal plants' crude extracts are more pharmacologically active than their constituent components. These herbal treatments have been shown to increase patient survival rates and lessen the toxicity and side effects of chemotherapy [5]. In the Indian Ayurvedic medicine system, as well as in Unani, Siddha, Chinese, and Greco-Roman medical traditions, polyherbal mixtures have been used to treat diseases from ancient times. Polyherbal formulations, which combine two or more herbs, are often preferred over single-herb treatments due to their enhanced therapeutic efficacy. The active component of a single herb may not be sufficient for pharmacological action. There is only limited scientific evidence on the action of polyherbal mixtures against diseases. Polyherbal combinations may act synergistically, increasing therapeutic effect and reducing toxicity [6]. Studies should continue on *in vivo* experimentation and clinical trials to integrate traditional medicine into modern treatment for patients. The effect and mechanism of numerous plants and polyherbal mixtures against various squamous carcinomas are the main topics of this review.

2. Anti-Cancer Effects of Medicinal Plants against Squamous Cell Carcinoma

About 65-80% of people worldwide still use traditional medicine as their primary source of healthcare. Affordability, accessibility, and cultural precepts are the key justifications for its use. According to the World Health Organization, the majority of people rely on herbs for their medical needs [7]. Throughout centuries, communities have used plants and herbs to treat disease and promote wellness. Today's contemporary medical system prescribes several plant-derived medications. Several plant-based medications have been found to have anti-tumor effects and the capacity to strengthen patients' immune systems. The use of dietary and herbal phytoconstituents as new therapeutics for treating different types of cancer revealed antiproliferative activity through a variety of actions, such as the inhibition of PEG-2, suppression of COX-2, induction of JNKs and MAPKs, cell cycle arrest, activation of oncogenes, decrease in mitochondrial membrane potential, and increase in ROS [8].

Turmeric has phytochemical curcumin and shows anticancer activity against oral squamous carcinoma [9]. 1- acetoxychavicol acetate, which is found in Malaysian ginger, causes apoptosis, prevents nuclear factor-κb from activating, and lowers the expression of cyclin D1 and COX-2 in oral squamous cancer cell lines [10]. *Ocimum sanctum* was reported to have anticancer activity against head and neck squamous cell carcinoma by inhibiting matrix metalloproteinase activity [11]. It also showed anti-cancer activity against the oral squamous carcinoma cell line. *In vitro* and *in vivo* studies using animal models of squamous cell carcinoma have shown potential anticancer efficacy for turmeric, blueberries, cranberries, bitter melon, neem, black pepper, and ginger. Phytochemicals such as vincetin, curcumin, nibolide, anthocyanin, and piperine are secondary metabolites that have demonstrated effectiveness against oral squamous cell carcinoma. These plants and phytochemicals induce apoptosis, upregulate p53, block the notch signaling pathway, disrupt cell migration, cell signaling, and arrest the cell cycle [12]. By inducing apoptosis, the dimethoxyflavone cirsimaritin from Ocimum sp. Inhibited the lung squamous cell lines [13]. On SCC 25 cell lines, water extract of Graviola leaf exhibits encouraging cytotoxic activity and cell inhibition in the G2M phase of the cell cycle [14].

A list of plants shown to have anticancer properties against various squamous carcinomas is provided in Table 1. Medicinal plants and their products have been reported against various cancer cell lines.

Table 1. List of plants and their phytochemicals that showed activity against squamous cell carcinoma.

Sl. No	Plant name	Plant extract/active components	Type of cancer cell line	Mechanism of action	Ref.
1.	*Allium sativum*	Allicin	OSCC	Apoptosis	[15]
2.	*Andrographis paniculata*	Andrographolide	HSC-2	Caspase-3 activation	[16]
3.	*Artemisia annua L*	Chrysosplenol D	SCC-9	Triggers Apoptosis Protein Kinase Signaling	[17]
4.	*Azadirachta indica*	Gedunin	SCC131	G1/S phase cell cycle arrest	[18]
5.	*Cinnamomum tenuifolium*	Essential oil Tenuifolide B	SCC-25 Ca9-22	Attenuating epidermal growth factor receptor-tyrosine kinase. Apoptosis, ROS Generation, Mitochondrial Depolarization, and DNA Damage	[19,20]
6.	*Coscinium fenestratum*	berberine	HN31	Apoptosis	[21]
7.	*Curcuma longa*	Curcumin	HSC3	Autophagy Apoptosis	[22]
8.	*Cynara scolymus*	Leaf extract	SCC-25	Apoptosis, Cell cycle arrest at G2/M phase	[23]
9.	*Daphne genkwa Sieb.*	Hydroxygenkwanin	OCEM 1 NSCLC	Induced cell cycle arrest	[24]
10.	*Euphorbia tirucalli*	Euphol	SCC 25	Decreases its proliferation	[25]
11.	*Imperata cylindrica*	Alkaloids	SCC-9	Cell cycle arrest G2/M phase. Cell death by apoptosis	[26]
12.	*Ocimum sanctum*	Leaf ethanolic extract	-	Inhibition of lung cancer	[27]
13.	*Piper nigrum*	Piperine	SCC9, SCC25, SCC4 KB cell line	Cell Cycle Arrest and Mitochondrial Oxidative Stress	[28]
14.	*Scutellaria baicalensis*	Root extract Flavanoids	HSC2,3,4, SAS	Cytostatic and apoptotic effects,	[29]
15.	*Scutellaria radix*	Flavanoids	SCC-25	Induced apoptosis	[30,31]
16.	*Vanilla Planifolia*	Leaf extract	A431	Antiproliferative and Apoptotic	[32]

The phytochemicals' anticancer effects are mediated by several pathways, including apoptosis induction, anti-inflammatory effects, and antioxidant effects. This biochemical and molecular mechanism strengthens these compounds' pharmacological activities. Avenues for the treatment of cancer are made possible by a thorough understanding of these mechanisms.

3. Mechanistic Action of Phytoactive Constituents Against Cancer

Numerous phytochemicals, such as phenolics, function as angiogenesis inhibitors and prevent the spreading of tumor cells. Numerous *in vitro* and *in vivo* investigations have advanced our understanding of the initial mechanisms underlying the antiangiogenic effects of phenolic compounds. Blocking the phosphorylation of the platelet-derived growth factor receptor, vascular endothelial growth factor receptor, and epidermal growth factor receptor prevents angiogenesis [33]. The phenolic component of green tea, EGCG, can chelate ferrous ions and inhibit the proliferation of hypoxia-inducible factor-1a-triggered cancer cells. Previous research indicates that EGCG inhibits the migration and proliferation of oral cancer cells, which is associated with reduced phosphorylated EGFR expression [34]. Numerous dietary polyphenolic compounds interfere with the adhesion and migration of tumor cells through various pathways, resulting in anti-invasive and anti-metastatic effects. The main flavonoid ingredient in onions, quercetin, caused cytotoxic effects and inhibited cancer cells' motility and invasion.

The most prevalent form of programmed cell death, apoptosis, is used as a therapeutic target for many malignancies. Apoptosis induced by several herbal substances demonstrated the suppression of carcinogenesis. Treatment of SCC-25 cells with alcoholic seed extract from *Acacia catechu* resulted in cytotoxicity with an IC_{50} value of 100 μg /ml. Following treatment with the above plant extract, the expression of the apoptotic markers caspases 8 and 9, cytochrome C, and Bax genes considerably increased, indicating the induction of apoptosis in SCC-25 cells. Bcl-2 gene expression was significantly downregulated as a result of this therapy. The apoptotic induction caused by extract treatment in SCC-25 cells is further confirmed by staining with AO/EB and PI, which reveals membrane blebbing and nuclear membrane deformation [35].

In contrast to the control, *Cynara scolymus* L. extract caused cell growth to cease in the G2/M phase, leading to a substantial rise ($p < 0.05$) in SCC-25 cells [23]. In SCC-25 cell lines, resveratrol has been found to impede DNA synthesis and cell proliferation. Resveratrol and quercetin together can intensify quercetin's ability to suppress cell proliferation [9]. Significant phytochemicals activate signaling pathways that control autophagic cell death in cancer. Inducing apoptosis and then autophagic cell death in SiHa cells was achieved using the chloroform fraction of the algal species *Chaetomorpha linum* [35].

The organic substances found in plants may inhibit the development of cancer in several ways. Phytochemicals can target the extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) pathways, which regulate cellular development and survival. The Akt/PI3 signaling pathway plays a critical role in both the development and prevention of cancer. Several biochemical actions, including NF-B activation and the phosphorylation of serine/threonine kinase 1, are regulated by epidermal growth factor (EGF) levels and promote unregulated cell proliferation and resistance to apoptosis.

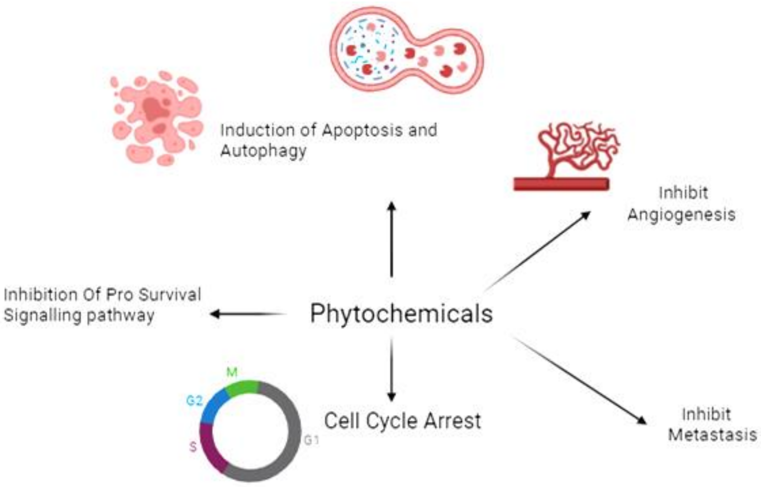

Figure 1. Various mechanistic actions of phytochemicals. (Biorender.com).

By blocking JAK/STAT signaling and activating apoptotic cascades, plant-derived compounds dramatically promote cell death across a variety of cancer types. The activation of transcription factors that regulate cell growth, vitality, and migration is triggered by the binding of Wnt proteins to the frizzled family of transmembrane receptors and by the accumulation of β-catenin in the nucleus. The apoptotic cascades are enhanced by the tumor suppressor protein p53 [33] (Figure 1). Cytotoxic agents are demonstrated through the study of the molecular processes by which phytochemicals combat disease. The active phytochemical components of individual plants are insufficient to produce the desired therapeutic effects. When numerous herbs are combined in precise ratios for polyherbal and herb-mineral formulations, the medicinal effect is enhanced and toxicity is reduced [36]. As a result, herbal mixtures can be utilized as medicine.

4. Polyherbal Mixture for Cancer Treatment and Prevention

Herbal products have been used universally as therapeutic agents for the treatment of ailments or as dietary supplements. Because of their extensive availability, low cost, and the widespread perception that they are safe to consume, primarily because they are made from plants or natural extracts, herbal medications continue to be widely used. The crude extract of medicinal plants has greater potential than a single isolated compound due to its synergistic effects [36].

The majority of polyherbal substances are used in Ayurvedic medicine to treat a variety of infections. Ayurvedic doctors frequently recommend Indukantha Ghritha (IG), a polyherbal remedy containing 17 plant parts, for a variety of diseases. The polyherbal medication significantly restored myelosuppression caused by cyclophosphamide. The Ayurvedic medication IG serves as a multipotent inducer of immune responses by promoting leukopoiesis and activating the host's non-specific and specific immune systems, as reported [37]. Many types of research focus on the study of polyherbal formulations against different cancers (Table 2). These are used in Ayurveda, Siddha, and Unani systems of medicine.

Table 2. List of polyherbal formulations used against squamous cell carcinoma at the different anatomical sites.

SL. No	Product name	Plant used	Type of cancer cell line	Mechanism of action	Ref.
1.	V2S2	10 plants	SCC40	Apoptosis	[39]
2.	PHF	*Aloe vera, Citrus aurantium, Curcuma longa, Emblica officinalis, Zingiber officinale,* Castor oil	A431	Apoptosis	[40]
3.	Maha Vallathy Leghiyam	*Aegle marmelos, Zingiber officinale, Plumbago officinale, Piper nigrum, Piper longum, Piper cubeba, Crocus sativa, Cinnamomum camphora, Cuminum cyminum*	KB	Apoptosis	[41]
4.	Neeradi Muthu Vallathy Lehiyam	*Semecarpus anacardium, Hydnocarpus kurzii, Smilax china, Calamus rotang, Nigella sativa, Cuminum cyminium, Acorus calamus, Indigofera aspalathoides, Azima tetracantha, Corallocarpus epigaeus, Withania somnifera, Enicostemma littorale, Calatropis gigantia, Ficus racemosa, Boerhaavia diffusa, Toddalia asiatica, Wrightia tinctoria, Sesamum indicum, Indigofera tinctoria,* and *Azadirachta indica*	KB	Apoptosis	[41]
5.	Praneem	*Azadirachta indica Sapindus mukerrossi*	HPV	Cancer preventive	[42]
6.	Panchavalkala	*Ficus bengaenesis Linn, Ficus glomerata Roxb., Ficus religiosa Linn., Thespesia populanea Ficus lacor Buch-Ham.*	SiHa	Induced cell cycle arrest	[43,44]
7.	Basant	*Curcuma longa linn, Emblica officinalis, Sapindus mukorossi Gaertn. Aloe barbadensis miller,* Rosa damascena	HPV	Cancer prevention	[45]
8.	Polyherbal Syrup USP3	*Zingiber officinale, Artemisia vulgaris*	SCC	Prevention	[46]

Ayurvedic general practitioners regularly recommend Varunadi Ghritha to cancer patients who have finished chemotherapy and radiation to prevent the T Cell Receptor signaling pathway disease from returning. It is also used to treat tumors of the head and neck [38].

5. Mechanism of Action of Polyherbal Against Cancer

Anticancer substances interfere with signaling pathways that regulate angiogenesis, apoptosis, and cell cycle arrest, thereby inhibiting cancer cell growth (Figure 2). A few of these signalling pathways are the TGF-beta, PI3K-Akt, and Toll-like signalling pathways.. A single drug might focus on a single route. Nevertheless, polymers can simultaneously target several routes [6]. The Ayurvedic-coded polyherbal drug V2S2, comprising 10 different plants, proved to be efficient against SCC40 cell lines [39]. The polyherbal formulations of *Aloe vera*, *Citrus aurantium*, *Curcuma longa*, *Emblica officinalis*, *Zingiber officinale*, and Castor oil expressed *in vitro* cytotoxicity activity against the A431 cell line [40]. MahaVallathy Leghiyam (MVL) and Neeradi Muthu Vallathy Leghiyam (NMVL) against human oral cancer (KB) cells by inducing apoptosis [41]. Praneem', a polyherbal formulation, expresses 80% clearance of HPV 16 from the cervix. Hence, this polyherbal is advised as a protective measure against cervical cancer [42]. Panchavalkala is a well-known Ayurvedic polyherbal formulation that has been reported to be used against inflammation, to clear ulcers, dress wounds, as a douche in leukorrhea and other vaginal diseases. PVaq exhibited anticancer activity against HPV-positive cervical cancer cell lines. It decreased the viability of F. religiosa cells, one of the components of PVaq, which induced cell cycle arrest in SiHa [43-45].

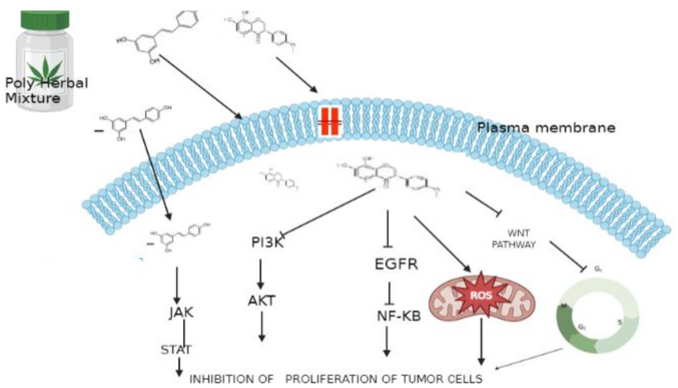

Figure 2. Mechanism of polyherbal mixtures against cancer. (Biorender.com)

A polyherbal syrup USP3 is a preventive medicine for skin cancer [46]. Habb-e-Ustukhuddus (HU), a traditional preparation, will be evaluated in 2023 for anticancer characteristics. This polyherbal mixture was shown to cause apoptosis (cell death) and prevent cancer cell migration and invasion, particularly in lung and breast malignancies.

One area of interest for research is the investigation of polyherbal formulations for cancer treatment. More research in this field is required, with an emphasis on various kinds and varied plant and product combinations. One should be careful to concentrate on incompatible combinations when creating polyherbal medicines. The plants selected should not be in viruddha combinations. Therefore, clinical trials must be conducted on polyherbal combinations before marketing. The benefits of polyherbal formulations include their high efficacy in treating a wide range of illnesses. They have a wide pharmaceutical range. They are also cost-effective, available easily, and natural [47]. A polyherbal combination of green tea, simvastatin, and curcumin showed potential to overcome resistance and improve therapeutic outcomes in oral SCC [48-50].

6. Limitations and Regulatory Process

In polyherbal formulations, there are limitations such as inconsistent sourcing of plant materials, seasonal challenges in collection, a very tedious isolation process, and difficulty in ensuring consistent potency across batches of sample formulations. Another constraint is limited clinical evidence, takes a long time to cure, and sometimes affects normal cells. In terms of safety, no higher level of toxicity has been reported for the natural product. The Food Safety and Standards Authority of India, a government agency in India, will allow us to commercialise the polyherbal products if we demonstrate, through in vitro, in vivo, in silico, and clinical trials, that they exhibit greater inhibitory activity against cancer. The Food and Drug Administration in the United States must approve the product for worldwide markets.

7. Conclusion

This review article discusses herbs, herbal products, and polyherbal formulations that can slow the proliferation of cancer, particularly squamous cell carcinoma. Through angiogenesis, immunity, apoptosis, and cell cycle arrest, polyherbal combinations demonstrate anticancer activity in vitro and in vivo, as well as in clinical studies against several cancer types. Even in palliative care or to lessen treatment-related side effects, these polyherbal combinations can be used. The synergistic impact of the compounds present gives the polyherbal formulation its advantage. A polyherbal formulation with synergistic effects shows greater activity against squamous cell carcinoma; its exact mechanism of action needs to be explored in clinical trials.

Author Contributions

Conceptualization, SAY; writing—original draft preparation, FSK; writing—review and editing, SAY; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

All the authors declare no conflict of interest.

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