Plant Derived Bioactive Compounds, Their Anti-Cancer Effects as an Alternative Target Treatment Strategy for Breast Cancer: An Updated Overview

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Abstract
For decades, cancer has been a major public health concern worldwide owing to its high mortality rate. Many therapeutic strategies have come up in the scientific world, but it’s pitiful to know that synthetic chemotherapeutic agents either cause adverse effects or cancer cells develop resistance to these agents. Plant-derived chemotherapeutic agents present a wide range of therapeutics and most are yet to be discovered. In the current review, we have discussed the tumoricidal properties of Mucuna pruriens (seed), Withania coagulans (berry), Anacyclus pyrethrum (rhizome), Arachis hypogea (leaf), Rhizoma polygoni (root) and Terminalia chebula (fruit). We have also tried to summarize the latest research in cancer chemoprevention and treatment using the bioactive components from these natural plants. Pharmaceutical developmental challenges and opportunities in bringing the phytochemicals into the market are also explored. The authors wish to expand this research area not only for their scientific soundness, but also for their potential-yet-affordable druggability.

Keywords: Chemotherapeutic, Mortality, Mucuna pruriens, Withania coagulans, Anacyclus pyrethrum, Arachis hypogea, Rhizoma polygoni, Terminalia chebula

1. Introduction

Cells have a marvellous mechanism of replacing the old and damaged with the new and healthy ones. In the course of performing this task some cells undergo certain changes at the genetic and epigenetic levels which prompt them to multiply uninterruptedly [1]. This ongoing, wild and unwanted growth of cells is described as a “tumour”. The tumour cells basically have minimal nutritional requirements and lose their attachment properties to other cells and the extra cellular matrix (ECM). This loss of anchorage helps them to flow throughout the body along with the liquid connective tissues, blood and lymph, causing what we know as the “metastasis” or spread of tumour cells to other sites of the body. Resulting in a state of malignancy which is now called as “cancer” instead of tumour. The lymph nodes of underarm,
2. Breast Cancer treatment

Breast cancer can occur in almost any cell type of the body. Breast adenocarcinoma is one such type of cancer which can occur in any part of breast whether in ducts which carry milk or glandular lobule which release milk. Depending on the origin, it can be further categorized into invasive (that spread to adipose and connective tissue of breast) and non-invasive cancer (ductal and lobular cancer) [3] (see Table 1, Figs. 1–9).

According to the American Cancer Society, breast cancer will be detected in around 284,200 American women in the year 2021. Owing to the fact, it is evaluated that nearly 44,130 American women will lose their life as the consequence of breast cancer in the same year [4]. If we throw the light on the statistics provided by GLOBOCAN project of breast cancer prevalence in India, it is unveiled that 17.3 lakhs Indian women were suffering from breast cancer in the year 2020 [5]. Although, breast cancer is age related disease whose risk increases with increasing age, retraction of cancer also depends on various other aspects that may be inherited or acquired during the course of one’s life. Inherited factors include the changes in genetic makeup of genes like BRCA1, BRCA2 and p53 which results in the loss of their function of regulating growth and suppressing tumor formation [6]. Alteration in other genes that regulate the hormonal balance and metabolism activity also ends up in contracting breast cancer.

Women who are living in vulnerable environmental conditions like exposure to heavy metals, pesticides and several man-made chemical compounds like diethylstilbestrol, whose structure is similar to the human hormone estrogen are at extreme risk of contracting breast cancer [7]. Furthermore, an inappropriate lifestyle also heightens the likelihood of tumorigenesis. This includes alcohol consumption, tobacco smoking, obesity, lack of physical workout and improper dressing habits [8,9].

2. Breast Cancer treatment

Early diagnosis and efficacious remedies will help in lessening the burden of cancer and its spread from one generation to another. At present, there are numerous ways to get rid of breast cancer as shown in Fig. 1. These treatment methods are mainly based on surgical removal of the tumor lump (lumpectomy or partial mastectomy), killing tumor cells by exposing them to harmful ionizing radiations (radiotherapy), tumor cells killing drugs (chemotherapy) [10]. Newer methods kill the tumor cells specifically without affecting normal cells thus called targeted therapy. Researchers have now found a way to stimulate the immune system of the patient so that patient’s immune cells will invade cancerous tissue and induce their apoptosis. This strategy is called immunotherapy aka biotherapy. These therapies are sometimes used individually or with combinations of one another as decided by the doctor depending on the patient’s stage [11].

The use of surgical methods to remove a tumor from the breast is a common way but it is helpful only if the tumor is limited to the breast. If lump is confined to a part of breast, then it can be removed while conserving the breast through a surgical procedure commonly called lumpectomy. Removing lump of tumour does change the breast shape and size. If the tumour has invaded to most parts of breast, it is advised to remove the breast completely, by mastectomy, including the involved lymph nodes to prevent its invasion to other body part [12].

Second approach of killing tumour cells is by exposing the cells to high energy ionizing radiations. As they break the DNA, it would result inhibition of cell proliferation. Depending on the size, location and type of tumour radiation can be given externally (outside body), internally (by placing the implant releasing radiations within the tumour), systemic. In order to prevent the recurrence of tumour, it is recommended to undergo radiotherapy after surgery [13].

Third widely applied tactic for killing overgrowing tumour cells is chemotherapy in which drugs are given orally or intravenously to specifically kill rapidly growing cells by arresting one of their cell cycle phases. Chemotherapeutic drugs are classified into several categories depending on their working mechanism, and chemical nature. They are:

a. Cyclophosphamide, cisplatin are the common alkylating agents that cross links the DNA and thus block cell cycle [14].

b. Some plant-derived agents inhibit microtubule formation to prevent cell cycle progression and these agents are known as taxanes. Common microtubule inhibitors used are paclitaxel, Docetaxel and many more [15].

c. Agents that alter the synthesis of the DNA and RNA monomers are the termed as anti-metabolites. Application of anti-metabolites like 5-fluourouracil (5-FU), Capecitabine, Methotrexate are used to block the cancer cell cycle progression in the S-phase [16].
<table>
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<tr>
<th>Sl no</th>
<th>Plant selected</th>
<th>Part</th>
<th>Phytochemical structure</th>
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<tr>
<td>1</td>
<td><em>Mucuna pruriens</em></td>
<td>Seed</td>
<td><img src="image" alt="Structure of L-DOPA" /></td>
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<td>2</td>
<td><em>Withania coagulans</em></td>
<td>Berry</td>
<td><img src="image" alt="Structure of Withanolide" /></td>
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<td>3</td>
<td><em>Anacyclus pyrethrum</em></td>
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<td>4</td>
<td><em>Arachis hypogea</em></td>
<td>Leaf</td>
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<td>5</td>
<td><em>Rhizaoma polygoni</em></td>
<td>Root</td>
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<td>6</td>
<td><em>Terminalia chebula</em></td>
<td>Fruit</td>
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d. Antibiotics are used to fight infection but some can be used to deal with the cancer progression like Epirubicin, Doxorubicin. They impede the activity of enzymes involved in DNA synthesis and are collectively called as anthracyclines [17].

During the replication of DNA in S phase, enzymes like topoisomerase unwind DNA by single or double-strand break to prevent DNA tangling. To hamper the DNA replication and ultimately cell cycle, these enzymes can be targeted using agents like camptothecin, Etoposide [18].

In most of the incidences of cases recorded, tumor cells of the breast express membrane receptors for estrogen and progesterone. Thus, high levels of these hormones enhance their proliferation rate. Researchers have come up with a way to control this proliferation by inhibiting this hormone-receptor binding. Such inhibition can be attained by using compounds that compete with estrogen (i.e., selective estrogen receptor modulators like tamoxifen), by destroying estrogen receptors (i.e., selective estrogen receptor down regulator like fulvestrant), by ceasing estrogen production (i.e., by aromatase inhibitors like anastrozole), or by removing the ovaries [19].

The last beautiful approach to killing breast cancer cells is immunotherapy where antibodies synthesized against the receptors specifically expressed by cancer cells are used to target them. One of the good examples of this is Trastuzumab which is humanized monoclonal antibody with G1 isotype and specifically binds to the human epidermal receptor 2 (HER2) [20]. This protein–protein binding blocks the signaling pathways leading to cell multiplication, thus stimulating apoptosis. According to the American Cancer Society, some of the developed monoclonal antibodies, anti-angiogenic drugs and immunotherapy are under clinical trials.

The negative impact of these medications is that they often kill the important proliferating cells like that of blood cells and hair follicles, leading to decreased immunity, weakness and hair loss. Radiation therapy to amounts to swelling of the breast, skin reaction and bone weakness [21]. Further, hormonal therapy leads to damaged ovaries, loss of appetite and joint pain. Immunotherapy can cause allergic reactions like flu, skin rash and also decrease in immunity. Prolonged usage of antibiotics can induce antibiotic resistance in cancer cells. Furthermore, it is noted that, use of cytotoxic drugs during pregnancy causes birth defects in babies.

After assessing all these treatment strategies and their adverse effects, scientists are now working hard to find the natural remedy to treat breast cancer. For ages, nature has blessed us with remedies for all the health problems. Plants in this regard offer a huge amount of promising potential as they synthesize secondary metabolites which can be non-toxic therapeutic agents to kill cancer cells [22].

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Fig. 2. Structure of A: Paclitaxel or Taxol and B: Vinblastine.
3. Active compounds that show anti-cancerous activity

To treat breast cancer, scientists have already found many metabolites obtained from plants which are now marketed in various formulated forms. The mechanism of killing cancer cells for each metabolite is different. Some toxins like taxol; alkaloids like vincristine and vinblastine inhibit microtubule depolarization, thereby prohibiting uncontrolled growth of cells as shown in Fig. 2. Medicinal plants represent an indispensable resource of pharmacologically active compounds with complex molecular structures. The cytotoxic and antitumor activity of these compounds results from various mechanisms, such as their activity on cytoskeletal proteins, which play a main role in cell division, inhibition of DNA topoisomerases, anti-protease or anti-oxidant activity and many others. Furthermore, medicinal plants and their biologically active compounds are useful to fight cancer by strengthening the immune system, decreasing side effects of synthetic anti-cancer drugs, overcoming resistance to chemo- and radiotherapy, exerting synergistic drug interactions in combination with other drugs, etc.

Biologically active compounds from medicinal plants frequently target tumor cells by several mechanisms, resulting in the inhibition of carcinogenesis, angiogenesis, oxidative stress, and induction of cell cycle arrest, extrinsic and intrinsic apoptosis, autophagy, or differentiation.

Paclitaxel (Taxol®) is the microtubule inhibitor that is derived from leaves of Taxus spp. plants. Its clinical trial was approved and was allowed to use for therapy against breast cancer in the year 1994. In the new formulation Abraxane®, paclitaxel is bound to albumin to improve its efficiency. Also, in 2007 nanoparticle made by polymeric crosslinking of paclitaxel was used in India which proved to be efficient over generic drug.

4. Selection of plants

Plant-derived drugs are desired for anti-cancer treatment as they are natural and readily available. They can be readily administered orally as part of patient’s dietary intake. Also, being naturally derived compounds from plants they are generally more tolerated and non-toxic to normal human cells. If plant-derived drugs can demonstrate
selectivity in research, are non-toxic to normal cell lines and show cytotoxicity in cancer cell lines, these drugs can be lead into clinical trials for further therapeutic development [9]. At present, Sulphoraphane, Paclitaxel, Vincristine and Pomiferin derived from Brassica, Taxus brevifolia, Catharanthus roseus and Maclura pomifera are under research and clinical trial stages of drug discovery [7]. Despite decades of investigations by the scientific community, so many potential plant candidates to cure cancer have been hidden in nature’s lap and remain to be unveiled. Some of these plants which are used in day-to-day life for their different advantages can offer cancer therapy. Six of these plants that are considered to be studied in this project are Mucuna pruriens, Withania coagulans, Anacyclus pyrethrum, Arachis hypogea, Rhizaoma polygoni, and Terminalia chebula (Table 1).

4.1. Mucuna pruriens

*M. pruriens* is a herbaceous, leguminous plant well known for its medicinal use in ayurveda. It has been taxonomically included in the family of legumes i.e., Fabaceae also known as Leguminosae or Papilionaceae; order Fabales; class Magnoliopsida and phylum Magnoliophyta [25]. The Indian system of traditional medicine has noted it as the “Magic bean” but it is also recognized by different names in different areas, as Koonchbeej in hindi, Velvet bean or Cowitch in English, Atmagupta in Sanskrit, Poonaiakkai in Tamil, Alkushi in Bengali, Khaajkuiri in Marathi, Kari NasguniBeeja in Kannada [26].

It is mainly found in tropical and subtropical regions of Africa and South Asia where the climate is warm and humid. As many as 150 species of *Mucuna* have been characterized till now. Traditionally it was grown for its use as food and feeding in China and India as it is a rich source of dietary proteins [27].

4.1.1. Biological description

This herbaceous annual twining shrub is approximately 15 m long with trifoliate, ovular-shaped hairy leaves and white or purple flowers that hang in clusters. The 2 to 3 or many flowers that have curved petals are arranged on the flower head of about 6–15 inches along with leaves forming drooping racemes. Commonly the flowers are bisexual actinomorphic with a simple pistil having a superior ovary, two or more marginal ovules and multiple stamens that can be distinct or united. At its young stage, it is which is fully covered with fuzzy hairs which shed when it grows old [28].

The pod of this plant is sigmoid and turgid with a length of 4 to 13 cm and about 1 to 2 cm wide (Fig. 3). It is covered with pale brown hairs and contains 4 to 6 ovoid-shaped seeds which are generally black in color. Due to the presence of mucunain and serotonin, these fuzzy hairs cause severe itching and irritating blisters when someone touches them [29].
4.1.2. Phytoconstituents

Mucuna holds lavish amounts of carbohydrates (42.7–64.8%), proteins (24–31.1%), lipids (4.1–14.39%), fibre (5.3–11.5%), several minerals like potassium (806–2790 mg/100 g), calcium (104–900 mg/100 g), and phosphorus (98–498 mg/100 g) [30].

Besides these nutritional components, Mucuna species contain ample amount of tannins, alkaloids, glycosides, saponins and other secondary metabolites. Seeds of this plant have been reported to contain several non-protein amino acids and essential oils. Strikingly, researchers have found that it possesses high levels of 3-[(3,4-dihydroxyphenyl)-l-alanine (l-DOPA). l-DOPA is one of the non-standard amino acid which is precursor of catecholamine neurotransmitters and hormones like dopamine, nor-epinephrine and epinephrine and is responsible to uplift the mood, and fight-or-flight responses [31]. Siddhuraju, in 2001, through the use of reversed-phase chromatography found that seeds of M. pruriens have ~5% of l-DOPA. In addition, the seed extract has also been reported to contain other compounds like glutathione (tripeptide), gallic acid (phenolic acid), beta sitosterol (plant sterol) and oils like palmitic acid, stearic acid, oleic acid, squalene, ascorbic acid, octadecanoic acid [32].

L-3-carboxy-1,2,3,4-tetrahydroisoquinoline, (→)-1-methyl-3-carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, dimethyl-3-carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and (→)-1,3-carboxy-1,7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline forms the major types of alkaloids presents in the seeds. Other alkaloids are mucunine, mucunadine, prurienine, prurieninine. Furthermore, the seeds also hold trace amounts of tryptamines like serotonin (5-hydroxytryptamine), nicotine, bufotenine (5-hydroxydimethyltryptamine), 5-methoxy-N, N-dimethyl tryptamine-n-oxide (5-MeO-DMT-n-oxide) and beta carboline [32].

In contrast to seeds, leaves of M. pruriens contain lesser concentration of l-DOPA i.e., about 0.5%. Considering tryptamines, leaves contain 0.006% dimethyl tryptamine (D,MT), 0.0025% N, N-Dimethyltryptamine (5-MeO-DMT) and 0.003% N, N-Dimethyltryptaminen-oxide (D,MT n-oxide). According to Dr. Duke phytochemical database, Mucuna leaves also contain trace concentration of compounds like 6-methoxyharman, genistein, hydroxygerinestin [33].

4.1.3. Pharmacology

Since time immemorial Indians have been using M. pruriens as ayurvedic medicine for its ability to cure many health disorders mainly those related to the urinary tract, gastro intestinal tract, nervous system and reproductive health. The entire plant provides a huge range of therapeutic potential. The most prominent seeds of this species are used to cure Parkinson’s disease due to the presence of a good concentration of l-DOPA. l-DOPA is extracted from seeds and is formulated to prepare medication for patients suffering from PD. Seeds of this species have laxative effect; thus, it is used to cure constipation. Also, because of its anti-depressant, anti-helminthic, antispasmodic and aphrodisiac activity, it is used to cure depressive neurosis, helminthiasis, menstrual disorders (dysmenorrhoea & amenorrhoea), muscular pain and impotency [34]. Furthermore, studies have shown that the powder of Mucuna seeds can cure pulmonary tuberculosis, scorpion sting, snake bite and possess anti-microbial, anti-epileptic, anti-neoplastic and uterine stimulant properties [35].

Leaves and roots of this plant are aphrodisiac and diuretic and are reported to cure ulcers, inflammation,
haidi. Hairs present on the pods cause itching when came in contact, but ointment made from these hairs is used as a local stimulant and mild vesicant [33].

4.2. Withania coagulans

W. coagulans dunal which is popularly known as paneeroda in Ayurveda is a plant with high significance value. The shrub is known by various names, some of which are, Indian rennet, vegetable rennet in English, paneerdodi in Hindi, ninggush- uiqie in Chinese, Spiubajjain Afghan, khamjira in Punjabi and many more. The berry of this plant has an unusual property of coagulating milk because of which it is commonly used to prepare paneer in various parts of India, because of which plant is named so. It exhibits such property due to the presence of an enzyme called withanin. The plant belongs to solanales order, solanaceae family and has been further placed in physalease tribe [34]. The plant has its habitat in the south Asian countries i.e., specifically in the northwestern parts of India, Iran, Pakistan and Afghanistan.

4.2.1. Biological description

This highly branched shrub is about 2–3 m in length and the branches are veiled by grey-white colored flowers and leaves which appear to be grey because of the presence of undetachable greyish tomentum. The lanceolate oblong leaves are about 2.5–5.7 by 1–2.2 cm and are slightly tapered with short stalks. The plant flowers generally from the month of January to April and berries ripe till May. The flowers are dioecious that is they have male and female reproductive parts on different individuals and thus show polygamy [35]. The flowers are 7–12 mm long and forms axillary clusters. Berry of the shrub is about 1 cm long and wide which is covered by sepal in a crown-like manner (Fig. 4). Oval-shaped seeds are globose and yellow in color with a diameter of about 2.5 mm. Berry contains about 40–60 seeds [31].

4.2.2. Phytoconstituents

The main constituents of the plant for which it is famous are the milk coagulating enzymes mainly found present in berries. Seeds of this plant are significantly rich in fatty acids like oleic acid, linoleic acid, palmitic acid, stearic acid, steroids like dihydrostigmasterol and β-sitosterol and sugars like maltose, galactose and arabinose. Steroids along with various alkaloids are reported responsible for the plant’s hypoglycaemic activity [36]. Proline, valine, hydroxyproline, glycine, tyrosine and acidic amino acid constitute the major amino acid pool in the plant. Most of the observed activities are due to the presence of steroidal lactones which are also called withanolides [37]. To understand the meaning, the term withanolides can be segregated into two parts “withan” referring to the genus “withania” and “olide” meaning lactone. Thus, withanolides are steroidal lactones having a basic ergostane skeleton and chemical name C28-skeleton 22-hydroxyergosta-26-oic acid –22, 26-olide. Modification in the side chains or carboxylic group leads the formation of new withanolides. Currently, about 138 different types of witanolides have been isolated and characterized from different parts and species of Withania [38].

Although, withanolides are present across Withania spp., some are specific to the particular species like withaferin A is mainly found in Withania somnifera. W. coagulans mainly holds withanolides like coagulin F, Coagulin G, coagulanolides, withacoagulin. Their structures are elucidated by various bioanalytical techniques like spectrophotometry and chemically named as 27-hydroxy-14,20-epoxy-1-oxo-(22 R)-witha-3,5,24-trienolide; 17beta, 27-dihydroxy-14,20-epoxy-1-oxo-(22 R)- with a –2,5, 24-trienolide; (17S,20S,22R)-[14alpha,15alpha, 17beta, 20beta -tetrahydroxy-1-oxowitha-2,5,24- trienolide] and 20beta -hydroxy-1-oxo-(22 R)-witha- 2,5,24-trienolide respectively [39].

Apart from withanolides, alkaloids have been identified from different parts of the plant, but leaves form the major source of alkaloids. There are about 14 different types of alkaloids identified. Some of them are nicotine, somniferinine, withanine, pseudowithanine, and choline [40].

4.2.3. Traditional use

Due to the presence of so many secondary metabolites, this plant is of high therapeutic use. Fruits of this plant are sweet in taste and help in relieving flatulence and high blood pressure due to their diuretic nature. Ethnomedicinal shreds of evidence indicate that fruit phytochemicals have the potential to cure diabetes mellitus. Coagulin L extracted from this plant showed hypoglycaemic effect on diabetic rats [41].

Seeds show anti-inflammatory properties due to the presence of several alkaloids, flavonoids and withanolides. It was reported that alcoholic extract of this plant was also able to suppress the inflammation in rats which were induced by egg albumin and formalin. Also, withanolides are reported to bind with cyclooxygenases which play important role in inflammation and can inhibit its activity. Thus, they have the potential to replace non-
selective steroidal anti-inflammatory drugs [42]. Its anti-inflammatory properties can be harnessed by using it as therapy for rheumatoid arthritis, an inflammatory autoimmune disease.

Withanolides like Withacoagulin A, withacoagulin C, withacoagulin D, withacoagulin E, withanolide L, were recorded to induce apoptosis in tumor B-cell, HL-60 leukemia cells. They induce apoptosis by mitochondria mediated cytochrome c release and thereby activating caspase cascade. Winthaferin A has shown cytotoxic activity against head and neck carcinoma, human lung cancer cell line [NCI-H460], mouse Ehrlich ascites carcinoma. Apart from this it shows wound healing, anti-microbial, anti-fungal, immunosuppressive and anti-oxidant activities. It is also hepatoprotective. “Liv –52”, a hepatoprotective herbal medicine by the Himalaya Healthcare (Product code: HHS200), also contains extracts of W. coagulans and W. somnifera [43].

4.3. Rhizoma polygoni

Polygonum cuspidatum Sieb. et Zucc. is a perennial herbaceous herb. It belongs to the Polygonum genus of the Polygonaceae family, which grows in Asia and North America. It promotes blood circulation, dispels stasis, expels wind and dampness, dissipates phlegm, and suppresses cough by removing jaundice and clearing heat-toxin. Cough, hepatitis, jaundice, amenorrhea, leukorrhea, arthralgia, hyperlipidemia, scald and bruises, snake bites, and carbuncles are among the conditions for which it is widely prescribed [44].

4.3.1. Phytoconstituents

Its effects on hypertension, hyperlipidaemia, cardiovascular and neurodegenerative diseases have also been thoroughly studied, both in the lab and in the clinic. R. palygoni comprises a variety of chemical groups (Fig. 5). The main compounds in this plant are stilbenes like resveratrol and polydatin, as well as anthraquinones like emodin and its glycoside. It also has flavonoids like quercetin and (+)-catechin in it. Emodin, physcion, emodin 8-O-Dglu-copyranoside, 2-methoxy-6-acetyl-7-methyljuglone, citreorosein, (+)-catechin, polydatin, and resveratrol are the main active ingredients isolated from this plant [45].

4.3.2. Pharmacological activities

There have been several natural compounds discovered to have anti-HIV efficacy. Alkaloids, flavonoids, and polyphenols are examples of these compounds. It was discovered that a 70% EtOH extract of R. palygoni has anti-HIV activity [46]. Dental caries is an oral disease caused by a dental biofilm. Anti-biofilm agents such as chlorhexidine and antibiotics have been linked to undesirable side effects such as extrinsic staining and bacterial resistance. It is a promising alternative medication for dental caries prevention. This herb, which is mostly made up of physcion, emodin, and resveratrol, has been shown to improve fluoride activity against Streptococcusmutans (S.mutans) virulence [47].

Extensive research has shown that the R. palygoni extract or its main constituents have anti-inflammatory properties that can help patients with arthritis, hepatitis, or ALL. In a Freund’s complete adjuvant (FCA)-induced arthritis model, the anti-inflammatory effects of the ethyl acetate extract of R. palygoni were investigated and the studies suggested that this plant has potency in inhibiting rheumatoid arthritis [48].

4.4. Arachis hypogea

North-eastern Nigeria and northern Cameroon are the origins of groundnut. It grows in wild from central Nigeria to southern Sudan, and it is now cultivated throughout tropical Africa, as well as to a lesser degree in the Americas, Asia, and Australia. Arabic travelers documented its use as a pulse in West Africa in the 14th century. After the arrival of groundnut from the New World tropics, its value waned [49].

4.4.1. Biological description

The peanut, or groundnut (Arachis hypogaea), is a legume (or “bean”) plant (Fabaceae) (Fig. 6). The peanut was most likely first grown in Peru’s valleys. It’s a 30–50 cm (1.0–1.6 ft) tall annual herbaceous plant. After pollination, the flower stalk elongates, causing it to curve until the ovary reaches the ground, giving it the name “Hypogaea”.

The peanut, also known as groundnut, is a legume plant (A. hypogaea) belonging to the family Fabaceae. Virginia group, Spanish group, Runner group, Valencia group, Tennessee red and Tennessee white are some of the varieties available [50]. Peanuts have 30 basic nutrients and phytonutrients in them, with vitamins and minerals found in high numbers. Crude fiber, cellulose, water, crude protein, ash, and fat make up the hulls of peanuts. Acids, arachin, lecithin protein, flavonoids, betacarotene, amino acids, minerals, fat, carbohydrates, and other chemical constituents are contained in the plant. Antimicrobial, anti-fungal, antiviral, anti-oxidant, anti-cancer, antihypertensive, neuroprotective, antimutagenic, antiproliferative, and
anti-inflammatory are several of its pharmacological properties. Peanuts can aid in soil enrichment. Peanuts are legumes, which means their roots can fix nitrogen. Limines, plasters, soap, and lubricants all contain peanut oil. Roots are used as a source of renewable energy and for cosmetic purposes. Peanut allergy is the most common cause of food allergy-related death [51].

4.4.2. Pharmacological activities

The flavonoid decomposition compound 5,7-dihydroxychromone (DHC) is abundant in peanut shells. The pathogenic fungi Rhizoctonia solani and Sclerotium rolfsii were found to be inhibited by DHC. Several studies have found that DHC released from peanut shells has a role in suppressing pathogenic fungal infection and competing for plant growth, but not in promoting Bradyrhizobium growth.

Resveratrol is a compound contained in peanut butter. Rather than communicating directly with the virus, resveratrol tends to inhibit viral infection/replication by controlling inflammatory responses and cellular stress pathways [52]. To be more precise, resveratrol inhibits the NF-kB pathway activation in response to TNF while increasing p53 activation. Resveratrol is possibly increasing antiviral immunity by increasing the activation of p53, a cellular protein involved in type I interferon-mediated antiviral responses [53].

Resveratrol is a stilbene-type aromatic phytoalexin contained in peanuts that have been shown to have anti-cancer properties in vitro, in animal models, and humans. This compound’s anti-cancer activity is primarily due to activation of apoptosis through several pathways, as well as changes in gene expression, both of which result in a reduction of tumor initiation, promotion, and progression [54].

4.5. Anacyclus pyrethrum

Anacyclus pyrethrum, also known as Akkalkara in Hindi and Pellitory in English is used as a tonic and rejuvenator in Ayurveda (Fig. 7). This plant is mainly found in areas of the Mediterranean region and countries like Syria, Algeria and North Africa. It is also found in the northern parts of India. This dicotyledon plant belongs to family Asteraceae and many plants from the same family and genus like A. radiatus, A. valentines and A. clavatus have been proved to be of high remedial significance due to the presence of a diverse number of terpenoids and flavonoids.

In ancient times, it was served as a potent immunomodulator and aphrodisiac. Its root can stimulate the salivary gland, thereby extracting the bad fluids from the body and thus, it was used to cure catarrh. Apart from this, chewing of its leaves has proved to heal toothache and tongue and muscle paralysis [55].

4.5.1. Biological description

A. pyrethrum is an evergreen plant that grows along the ground and roots are buried inside the soil. The stems are procumbent and they are highly branched. The smooth leaves are pale green in color and petiolated and pinnate i.e., they remain attached to the stem and forms small leaflets.

The root of the plant is small in length, maxima up to 15 cm (Fig. 8). They are tough, cylindrical, brown in color and possess lots of grey hair on their surface. It is covered with a thin bark on its surface and it tastes aromatic and pungent. As the root of the plant is high of remarkable value, it is generally collected in the autumn season and stored in the dried form [56].

4.5.2. Phytoconstituents

Phytochemical screening done by various researchers provides us data that this plant is a rich source of secondary metabolites like tannins, alkaloids, coumarins and many more. The roots of the plants contain various alkaloids like pyrethrins and alkyl amides like isobutylamides and tyramine amide. Different alkyl amides are obtained depending upon the extraction method and solvent chosen [34]. Roots also possess inulin, volatile oils (spathulenol), fatty acids, sterols, anacyclin and sesamin. The yield of secondary metabolites also depends upon the growth conditions and harvesting period of the plant.

4.5.3. Pharmacology

In the ayurvedic system of medicine, the roots of this plant have been considered to have aphrodisiac activity and were used for vitality and virility. In an evaluation done by Vikas Sharma et al. in 2009, it was observed that male rats treated with the petroleum ether extract from the root of akkalkhara for 28 days, showed enhanced accessory sexual organs and sexual behavior. It is suggested that extract helps to improve the production and activity of androgens like testosterone [24].

4.6. Terminalia chebula

Root extract from this plant has proved to be used for enhancing memory as it improves neurotransmission from the central cholinergic system and
thus can help in some way to treat Alzheimer’s disease patients.

Alcoholic root extract from the plant acts as a good local analgesic and can be used during oral surgeries in low concentrations. Also, in research, it was found that such extracts were able to cure depression by interacting with the dopamine and adrenergic receptors thus, help in boosting noradrenaline and dopamine levels in the brain of rats [45]. Because of its exceptional healing abilities, *T. chebula* is known as the “king of medicines” and is often mentioned first in the Ayurvedic medicine system (Fig. 9). In Ayurveda, *T. chebula* is thought to be capable of destroying all diseases and eliminating all wastes from the body, as well as promoting tissue growth and health. *T. chebula* has been used in conventional formulations for anti-diabetic, anti-inflammatory, laxative, antibacterial, anti-fungal, cardiotonic, diuretic, hyperlipidaemic, and jaundice properties. Anti-helminthic, aphrodisiac, and restorative effects are also found in this herb [57].

4.6.1. Biological description

The *Terminalia* genus, which contains 250 species, is widely distributed in tropical areas around the world. *T. chebula Retzius* (*T. chebula* Retz.) (Family: Combretaceae), also known as black Myroblans in English and Harad in Hindi, is popular folk medicine that is native to India and Pakistan, as well as many other Asian and African countries. It has been studied for its homeostatic, antitussive, laxative, diuretic, and cardiotonic properties. At least seven *Terminalia* species have been used to treat cancer in the past [58,59].

4.6.2. Phytoconstituents

The plant’s fruit has a wide antibacterial and antifungal range, as well as inhibiting the growth of *E. coli*, the most common cause of urinary tract infection. Tannins, anthraquinones, chebulinic acid, chebulagic acid, chebulic acid, ellagic acid, and gallic acid are the main bioactive constituents of the fruit. Polyphenolic compounds, triterpene glycosides, terchebulin, punicalagin, terlavin-A, flavonoids such as rutin and quercitin, terpenene glycosides, arjungenin and arjunglucoside-I, and a trace amount of phosphoric, succinic, syringic, and quinic acids are among the other minor compounds [60].

5. Conclusion and Future prospects

As breast cancer is the leading cause of mortality in women and is also showing its occurrence among males, it is necessity of the time to discover the potent chemotherapeutic agent that would induce apoptosis in the breast cancer cells without showing any adverse effects. Through the extensive mechanistic studies, we have observed robust chemopreventive effects by some of the phytochemicals. As cancer chemoprevention and treatment using natural phytochemicals have been such an attractive approach, further efforts are fully justifiable to thoroughly understand their potencies, pharmacokinetic performances, pharmacodynamic responses, metabolisms, toxicities, drug–drug interactions, polymorphisms, and then formulations, stabilities and degradations, and dosage regimens. Natural dietary phytochemicals have been and will continue to be a promising and active research area in the near future.

Conflict of Interest

There is no conflict of interest.

References


