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Phytoalexins: Defend systems of plants and Pharmacological Potential - A systematic review

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Abstract
Plants are easily prone towards microbial infections on exposure to microorganisms and pathogens. In order to defense, plants produce low molecular weight secondary metabolites which were later known as "Phytoalexins". These molecules have vast therapeutic potential also. The purpose of this review is to explore the phytoalexins and their pharmacological effects. The data included from the articles were published from PubMed, Web of Science, Medline, Scopus, and Embase by using relevant keywords including plants possessing phytoalexins and their specific biological applications. phytoalexins started with progress in their biochemistry and bioorganic chemistry, resulting in the determination of their structure, their biological activity, as well as mechanisms of their synthesis and catabolism by microorganisms. This has led to potential applications for increasing plant resistance to diseases. Phytoalexins exhibit an enormous diversity belonging to various chemical families such as for instance, phenolics, terpenoids, furanoacetylenes, steroid glycoalkaloids, sulfur-containing compounds and indoles. phytoalexins are used in the various diseases and applications of plants and human health. Based on this review, it can be concluded that phytoalexins have tremendous potential in the treatment and prevention of various life-threatening diseases such as diabetes, cancer, brain damage and heart attack.
Key words: Antidiabetic, Lungcancer, **s**kin cancer**,** Brain cancer, Phytoalexins

Introduction

Plants face serious threat from plant pathogens mainly of microbial origin. Chemical control is an almost indispensable tool in the management of cultivated plant diseases and pests. The continued use of non-selective synthetic fungicides and insecticides in food crops is a global concern owing to their potential harm to human health and the environment [1].
Furthermore, the indiscriminate and excessive use of fungicides in crops is a major cause of the development of resistant pathogens populations, resulting in the application of high concentrations of these fungicides and the consequent increase in toxic residues in foodstuffs [2]. To improve this situation, researchers are actively exploring alternative methods of disease and pest control. Therefore, plants evolved many mechanisms to defend themselves from invading pathogens, producing thick cuticular wax and other forms of structural defences [3]. One of these alternative methods is the use of elicitors, compounds that can stimulate the induction of natural defense mechanisms of plants [1]. Induced defense involves the activation of latent resistance mechanisms in plants in response to pre-treatment with biotic and abiotic agents [4]. Induction responses include the synthesis and accumulation of phytoalexins (fungitoxic compounds) [5] and pathogenesis-related proteins (PRs) [6,7]. These compounds stimulate biochemical and physiological changes in plants during defense responses and protect against subsequent infections by pathogens [8].
In addition to this, plants produce certain antimicrobial substances during pathogen invasion that help them defend against pathogens. Phytoalexins (Greek words: phyton-plant and alexos - defend) play

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a role in plant defense and are absent in healthy plants [9]. Since the synthesis of phytoalexins is induced by specific substances like elicitors, these are referred to as species-specific substances.
A few hours or days after pathogen attack, phytoalexins are produced in small amounts and trigger a defense response in affected plants. It occurs in Solanum tuberosum inoculated with an incompatible strain of Phytophthora infestans induced the synthesis of defense-related metabolites that confer resistance to a compatible strain of the pathogen [10]. In 1940, these stimulated antibiotics were called phytoalexins, whose production was found to be trigged in response to P. infestance attack in potatoes [11,12], hence, the term phytoalexins was first applied for antimicrobial substances. Phytoalexins and phytoanticipins differ in terms of their production and response to invading pathogens. Eventhough, their production may appear arbitrary, this difference is based on fundamental difference in the responses of host plants to microbial invasions. Phytoalexin plays a vital role in plant disease resistance, when a pathogen induces an active response (that is induced upon exposure to the plant pathogen); A phytoanticipin plays a role in the plant immune response only through passive interaction (even without pathogen exposure).
Phytoalexins are less molecular weight, inducible secondary metabolites that have antimicrobial potential [9,13]. After plants are exposed to various biological factors such as fungi, bacteria, viruses, Physical factors such as heat shock, ultraviolet radiation, injury, heavy metals, or chemical factors such as phytoalexins are produced by denovo synthesis. The first phytoalexin was isolated from pea (Pisum sativum) after infection by Ascochyta pisi, and this phytoalexin was chemically characterized as (+)-pisatin.

Origin of Phytoalexins

The concept of plant phytoalexins was introduced about 70 years ago from potato tuber tissues infected by Solanum tuberosum i.e. Phytophthora infestans. The tuber tissue, in turn, produced certain chemicals, referred as phytoalexins, that inhibited the growth of microbes and protected the plant from later infections. Muller & Borger first submitted a paper on this hypothesis, then they experimented with another plant and demonstrated that plants produce such antimicrobial compounds when infected with pathogens [14].

Phytoalexins from Various Plant Families

Phytoalexins are synthesized by different plant families such as Apiaceae, Poaceae, Malvaceae, Solanaceae, Brassicaceae, Leguminosae, Vitaceae, Chenopodiaceae, Orchidaceae, Euphobiaceae, Convolvulaceae, Linaceae, Rutaceae, Rosaceae, Compositae. Various chemically active phytoalexins belong to different families including terpenoids, phenolics, furanoacetylenes, steroid glycolalkaloids, and indoles. The chemical diversity of phytoalexins is summarized in their plant family source (Table 1,2) [15-35].

Table 1.Phytoalexins from various families

S.No	NAME OF THE PLANT FAMILY	PHYTOALEXINS
1	Apiaceae	Falcarinol, Xanthotoxin, 6-methoxymellein
2	Poaceae	Sakuranetin, phytocassanes, phenylamides, apigeninidin, zealexins, kauralexins
3	Malvaceae	Terpenoids, gossypo
4	Solanaceae	Capsidiol, scopoletin
5	Brassicaceae	Camalexin, Brassinin, spirobrassinin, brassilexin, rutalexin
6	Leguminosae	Isoflavones, Isoflavanones, Isoflavans, Coumestans Pterocarpans/pisatin, phaseollin, glyceollin and maiackiain Furanoacetylenes/wyerone Stilbenes/resveratrol Pterocarpens

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7	Vitaceae	Resveratrol, viniferins, piceids, pterostilbene
8	Chenopodiaceae	Safynol, Betagarin, Betavulgarin
9	Orchidaceae	Loroglossol
10	Euphobiaceae	Casbene
11	Convolvulaceae	Convolvulaceae
12	Linaceae	Phenylpropanoids/coniferyl alcohol
13	Rutaceae	Methylated phenolic compounds/xanthoxylin
14	Rosaceae	Biphenyls/auarperin Dibenzofurans/cotonefurans
15	Compositae	Polyacetylenes/safynol

Table 2.Phytoalexins and their Natural food Sources

S.NO.	PHYTOALEXIN	NATURAL FOOD SOURCES
1	Capsidiol	Orange bell pepper, red bell pepper, green vegetables
2	Isoflavones	Soya foods, legumes including chickpeas, fava beans, pistachios, peanuts
3	Flavonoids	Nuts, whole grains, citrus fruits, apples, berries
4	Brassinin	Chinese cabbage, Brussels sprouts, and cauliflower
5	Resveratrol	Peanuts, pistachios, grapes, red and white wine, blueberries, cranberries
6	Sakuranetin	Cherries, plum, wild carrots, blackcurrants, black walnuts, walnuts
7	Pterostilbene	Almonds, blueberries, grape leaves, pterocarpus marsupium heartwood

Phytoalexin Enriched Foods

In the last 10 years, functional foods have created their niche in the market as they are beneficial to human health and are used to prevent lifestyle disorders such as diabetes, obesity, cancer, and various heart disorders. Phytoalexins have been researched many years ago as secondary metabolites with antimicrobial activity synthesized by plants to protect plants from various pathogen infections. Recently, phytoalexins have been studied in different plant-derived foods to provide nutritional and various health benefits. Since phytoalexins have been investigated to show different activities such as anti-inflammatory, anti-diabetic and anti-cancer activity, consumption of such phytoalexin-rich foods is expected to prevent and treat such diseases. Some of the phytoalexins are shown below along with their sources.

Treatment of Diabetes

Diabetes is a chronic disease characterized by hyperglycemia and is the most studied and prevalent disease worldwide. The underlying pathology of the disease involves insufficient secretion of insulin or insulin resistance, or both. From reducing glucose transporters to reducing the number of insulin receptors, this process leads to long-term damage to different organs such as the eyes, kidneys, heart and blood vessels, leading to diabetic complications. Resveratrol, a naturally occurring phytoalexin found in tea, wine grains, fruits, and vegetables, has shown potential as an antidiabetic agent. Based on research and in-vivo studies, resveratrol has been found to be an effective agent for reducing

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glucose levels in both type-1 and type-2 diabetes [36-38]. According to clinical trials, single dose and regular oral administration of phytoalexin for months improves insulin resistance. One mechanism behind this is that resveratrol activates sirtuin in beta cells, which lowers levels of insulin secreting protein-2 called Ul insulin reCP2 and overcomes insulin resistance. It also stimulates glucose uptake in the absence of insulin by increasing GLUT4 receptors on the plasma membrane. Cytokines damage insulin-producing pancreatic beta cells, and resveratrol inhibits cytokines, protecting the beta cells and reducing the unwanted release of insulin [39].

Diabetic Neuropathy

Neuropathy is a complication of type-1 and type-2 diabetes, resulting in pain, reduced mobility, and disabling disability. Induction of oxidative stress in diabetic neurons activates different biochemical pathways and causes damage. Activation of the transcription factor NF-κB by oxidative stress leads to the production of inflammatory mediators such as cytokines, TNF-α, interleukins, COX-2, which are indicative of nerve damage. Resveratrol acts by inhibiting transcription factors, which control inflammatory factors and improve neuropathic pain in diabetic patients [40,41].

Diabetic Nephropathy

Diabetic nephropathy is an important cause of kidney damage and is defined by increased urinary albumin excretion and affects patients with type-1 and type-2 diabetes. Complications show effects such as glomerular hypertrophy, proteinuria, reduced glomerular filtration, and ultimately impaired renal function.

Diabetic Retinopathy

It is one of the major diabetic complications affecting 150 million people worldwide. If not treated properly, the problem can lead to retinal damage and vision loss. This complication is caused by inflammation, oxidative stress and lipid peroxidation. The results of a study suggest that administration of resveratrol at a dose of 5mg/kg for 4 months effectively corrects the problem by lowering blood sugar levels and reducing retinal thickness. Another research study by Zeng et al. Rat models at doses of 5 and 10 mg/kg for 7 months gave positive results by inhibiting apoptosis in retinal cells induced by high glucose levels in diabetic patients [42].

Diabetic Liver Damage

The main pathology behind the complication is liver fibrosis, inflammation of the liver known as steatohepatitis and infiltration of intrahepatic fatty tissue. Improper treatment can lead to liver cirrhosis or liver cancer. A recent study found that oral administration of 20 or 40 mg/kg of resveratrol inhibited the activation of the NF-κB pathway and other inflammatory mediators, resulting in less chance of liver damage. Also, another study showed that resveratrol at a dose of 10 mg/kg for 15 days reduced blood glucose levels and the chances of liver damage by reducing oxidative stress [43].

Treatment of Various Types of Cancer

According to the data, cancer appears to be a threat and a global killer. It accounts for about 23% of all deaths in the United States and is the second most common disease after heart disease. Cancer is an abnormal growth of cells, which is caused by internal and environmental factors like diet, stress. Phytoalexins such as resveratrol and others have shown anticancer effects and may be used in cancer treatment. Phytoalexins inhibit the S and G2 phase of the cell cycle and effectively induce apoptosis in several types of cancer, such as leukemia, colon cancer, prostate cancer, and breast cancer [44].

Skin Cancer

The indole phytoalexin brassinin, first discovered as a major component of cabbage, has been shown to have anti-cancer properties. Later, it was synthesized and found to be effective against cancer. Phytoalexin was effective against skin tumor. This activity was observed in a 90-day study when the

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agent was administered to mice and gave positive results without side effects and toxicity. The mechanism of action of brassinin is not clear, but the unique structural properties of the compound with an indole nucleus and an isothiocyanate-based side chain give it excellent anticancer activity [45].

Breast Cancer

Breast cancer is a major health problem affecting women in both developing and developed countries. More than one million breast cancers are diagnosed each year. Resveratrol inhibits breast cancer by various mechanisms such as reducing the release of anti-apoptotic proteins such as NFκB, which inhibits cell growth by inducing apoptosis. Furthermore, it downregulates the gene expression of BCL-xl in HER-2 receptor positive and negative breast cancer cells [46].

Brain Cancer

Brain cancer has been an undertreated problem for years. The number of brain tumor patients in the United States has reached 43,800 per year. So far 12,690 patients have died from this disease. Resveratrol, which is active against many cancers, is also used in the treatment of brain cancer. Phytoalexin crosses the blood-brain barrier and reduces oxidative stress, reduces inflammation and induces apoptosis. Furthermore, resveratrol also activates p53, NF-B, Wnt, m-TOR to induce cancer cell death. Currently, resveratrol is used as a medical treatment and saves the lives of cancer patients [47].

Lung Cancer

The incidence of lung cancer is now increasing worldwide. Exposure to dust particles or respiratory illnesses can lead to this highly prevalent disease. Phytoalexins act against lung cancer by different mechanisms, suppressing the XRCC1 gene and showing a synergistic effect with etoposide [48]. It inhibited the proliferation of H838 and H520 cells. It also inhibits endothelial growth factor and AKT/m-TOR mediated pathways.

Treatment of Tumer Cells

In vitro studies on tumor cell lines and in vivo studies on animal models have revealed anti-estrogenic activity of glyceollins, demonstrated by suppression of estrogen-responsive tumors by affecting estrogen receptors. Further analysis of lipid and glucose metabolism emphasized the osteoinductive, antioxidant, antimicrobial and dose-dependent potential neuroprotective effect of glyceollins on central nervous system function. Glyceollins phytoalexins have been reported to play important roles in stimulating protein kinase, lipid kinase, and estrogen receptor signaling pathways [49]. Glyceollins have been reported to have antibacterial, antioxidant, antifungal, antinematode, antiestrogenic, antiproliferative, anti-inflammatory and anticholesterolemic potential. Because of their many health-promoting benefits, glyceollines are recommended as therapeutic/nutritive/dietary products.

Phytoalexins from model plants such as O. sativa and A. thaliana were tested for their potential therapeutic benefits. In an experiment to evaluate the cytotoxic effect of camalexin (an indole-type phytoalexin) on prostate cancer cells, it was found that more aggressive prostate cancer cells that express high levels of ROS (reactive oxygen species) are more sensitive to camalexin than those that are less aggressive prostate cancer cells [50]. (Smith et al. 2013). Besides camalexin, several indole-type phytoalexins have been found to have anticancer properties [51]. Whereas a rice methoxylated flavanone phytoalexin, i.e., sakuranetin is known to possess several antiproliferative, antidiabetic, antiviral, antimicrobial, antioxidant, anti-inflammatory, antimutagenic, antiparasitic and antiallergic properties [52-55].

Conclusion

Plants are susceptible to disease and in response they release chemicals called as phytoalexins or antimicrobial compounds. Phytoalexins synthesized by plants in response to pathogenic diseases and microbial infections show great importance in human health. They contribute to the treatment and

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prevention of various life-threatening diseases such as diabetes and cancers. Phytoalexins have anti-inflammatory and antioxidant properties that treat most ailments. Reduction of oxidative stress leads to disease management and control. Therefore, the review covers the recent applications of phytoalexin in plants, human health and disease.

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