



Phytoalexins: Sources and Their Pharmacological Potential

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ABSTRACT

Background: 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.

Purpose: The purpose of this review is to explore the phytoalexins and their pharmacological effects. **Methods:** The data included from the articles were published from Web of Science, PubMed, Medline, Scopus, and Embase by using relevant keywords including plants possessing phytoalexins and their specific biological applications.

Results: The review insights the potential of phytoalexins in various diseases and to explore phytoalexins applications in human health and disease control.

Conclusions: On the basis of this review it may be concluded that phytoalexins have tremendous potential in the treatment and prevention of various life-threatening diseases like diabetes mellitus, cancer, brain damage, and heart attack.

1. Introduction

Plants utilizes a complex defense mechanism against pest and pathogens, which lead to the production of low molecular weight secondary metabolites. These metabolites have antimicrobial property and are known as Phytoalexins (Egbonu et al., 2018). Once the microorganism invaded in the plant, the plant in response to the pathogen release the antimicrobial compounds known as phytoalexins in the infected sites. The biosynthesis of most of the phytoalexins is due to the induction of biotic and abiotic stress (Pedras et al., 2007).

The phytoalexins are not only activated in response to the microbial infection, but they can also be activated by abiotic stresses such as elicitation of UV-light, chemical mediators such as surfactants, antibiotics, plant regulators, heavy metal ions, or the chemical products released by the microorganisms.

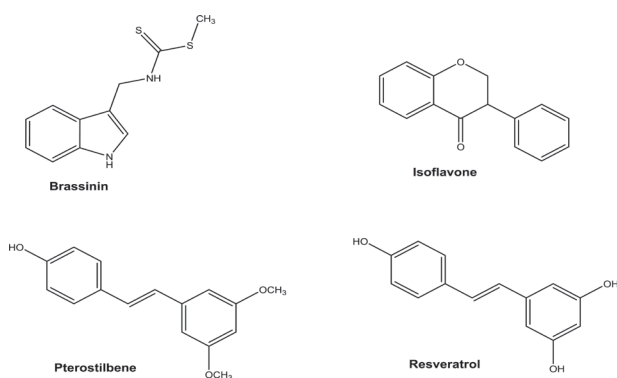
Phytoalexins contributed to the various pharmacological activities like antioxidant, anticancer, and cardiovascular activities. The biological activities of phytoalexins are enormous, this give a key idea to biologists and researchers to research on the potential of phytoalexins against various diseases (Grayer, 2001; Bavaresco, 2003; Pedras et al., 2006).

2. History of Phytoalexins

The concept of plant phytoalexins was introduced before 70 years ago from the *Solanum tuberosum* i.e. potato tuber tissue that had been infected by *Phytophthora infestans*. It was supposed that the tuber tissue, in response produced some chemicals now known as phytoalexins, that inhibited the growth of microorganism and protected the plant against later infections. Muller & Borger first presented the paper on this hypothesis and later on they experimented on another plants and demonstrated that plants produce such antimicrobial compounds when infected by pathogens (Hammerschmidt, 1999).

3. Phytoalexins from Different Plant Families

Phytoalexins are synthesized by variety of plants families like Fabaceae, Solanaceae, Vitaceae, Brassicaceae, Poaceae. Diverse chemically active phytoalexins belong to various families, including terpenoids, phenolics, furanoacetylenes, steroid glycoalkaloids, indoles. The chemical diversity of phytoalexins, their plant family source are summarized in (Table 1) (Suman, 2017).

**Table 1:** Phytoalexins from Different Plant Families.

S. NO.	PLANT FAMILY	PHYTOALEXINS	REFERENCE
1.	Amaryllidaceae	Flavans	(Coxon et al., 1980)
2.	Apiaceae	Falcarinol, Xanthotoxin, 6-methoxymellein	(Kello et al., 2014)
3.	Brassicaceae	Camalexin, Brassinin, spirobrassinin, brassilexin, rutalexin	(Browne, 1991)
4.	Chenopodiaceae	Safynol, Betagarin, Betavulgarin	(Geigert et al., 1973)
5.	Euphobiaceae	Casbene	(Sitton, 1975)
6.	Leguminosae	Isoflavones, isoflavanones, coumestants	(Jeandet et al., 2013)
7.	Malvaceae	Terpenoids, gossypol	(Lozano et al., 2014)
8.	Orchidaceae	Loroglossol	(Smith, 2014)
9.	Poaceae	Sakuranetin, phytocassanes, phenylamides, apigeninidin, zealexins, kauralexins	(Jeandet et al., 2013)
10.	Solanaceae	Capsidiol, scopoletin	(Jeandet et al., 2013)
11.	Vitaceae	Resveratrol, viniferins, piceids, pterostilbene	(Langcake, 1976)

4. Phytoalexin Enriched Foods

From last 10 years, functional foods have developed their place in the market because they are beneficial to human health, and are being used to prevent lifestyle disorders such as cancer, diabetes, obesity, and various cardiac disorders. Phytoalexins were researched many years ago as secondary metabolites with antimicrobial activity synthesised by plants to protect plants from various pathogenic infections. Recently, phytoalexins were investigated in various plant derived foods to provide nutrition and various health benefits. As phytoalexins were explored in showing various activities like anti-inflammatory, anti-diabetic, and even anticancer activity also, so by consuming such phytoalexins rich foods, it is expected to prevent and treat such diseases. Some of phytoalexins with their sources are showed below.

Table 2: Phytoalexins and their Natural food Sources (Boue et al., 2009).

PHYTOALEXIN	NATURAL FOOD SOURCES
Flavonoids	Nuts, whole grains, citrus fruits, apples, berries
Isoflavones	Soya foods, legumes including chickpeas, fava beans, pistachios, peanuts
Resveratrol	Peanuts, pistachios, grapes, red and white wine, blueberries, cranberries
Brassinin	Chinese cabbage, Brussels sprouts, and cauliflower
Pterostilbene	Almonds, blueberries, grape leaves, perocarpus marsupium heartwood
Capsidiol	Orange bell pepper, red bell pepper, green vegetables
Sakuranetin	Cherries, plum, wild carrots, blackcurrants, black walnuts, walnuts

5. Pharmacological Potential of Phytoalexins

5.1. Potential of Phytoalexins in Treatment of Diabetes Mellitus and its Complications

Diabetes mellitus is a chronic disease which is characterized by hyperglycemia, and a most studied and prevalent disease

in the whole world. The pathophysiology behind the disease involved insufficient secretion of insulin or insulin resistance or both. From reduction in glucose transporters, to the down regulation in the number of insulin receptors, the process leads to long term damage of various organs like eyes, kidneys, heart and blood vessels and cause diabetic complications.

A naturally occurring phytoalexin, resveratrol which is found in tea, wine cereals, fruits, vegetables shows potential of acting as an anti-diabetic agent. Based on research and in-vivo studies resveratrol was found to be an effective agent to lower glucose level in both type-1 and type-2 diabetes (Huang et al., 2020).

According to, the information from the clinical trials, the phytoalexin improves the insulin resistance on oral administration of single dose and regular dose for months. One of the mechanism behind that is, the resveratrol activates the sirtuin in beta cells which decreases the level of uncoupling protein-2 called UCP2 and overcomes the insulin resistance. Moreover, it also stimulates the glucose uptake even in the absence of insulin via increasing the GLUT4 receptors in the plasma membrane. Cytokines damages the pancreatic beta cells which are insulin releasers, inhibition of cytokines by resveratrol preserve the beta cells and reduce the unnecessary release of insulin (Öztürk et al., 2017).

Diabetic Neuropathy

Neuropathy is the complication of both type-1 and type-2 diabetes which results into pain, decrease in movement, and amputation. Induction of oxidative stress in neurons of diabetic patient activates various biochemical pathways and causes damage. Activation of NF- κ B a transcription factor by oxidative stress leads to the production of inflammatory mediators such as cytokines, TNF- α , interleukins, COX-2 which shows nerve damage. Resveratrol acts by inhibiting the transcription factors which leads to the down regulation of inflammatory factors and improves the neuropathic pain in diabetic patients (Kumar, 2007; Sharma, 2007).

Diabetic Nephropathy

Diabetic nephropathy is the major cause of kidney damage and is defined by increase in urinary albumin excretion and affect both type-1 and type-2 diabetic patients. The complications show effects like glomerular hypertrophy, proteinuria, reduced glomerular filtration, and lastly impaired renal function.

The results of preclinical studies shows that resveratrol decreases albumin concentration in urine, improves creatinine clearance, and reduce the size of glomerular

basement membrane and hence effective against diabetic nephropathy (Wen et al., 2013; Kim et al., 2012).

Diabetic Retinopathy

It is one of the major prevalent diabetic complication affecting 150 million people worldwide. If not treated properly the complication can lead to retina damage and vision loss. The complication occurs due to inflammation, oxidative stress and lipid peroxidation. One of the study gives results that by administering resveratrol at a dose of 5mg/kg for 4 months decreases the blood sugar level as well as reduces the thickness of retina and treat the complication effectively. Another research study by Zeng et al. on rat models at a dose of 5 and 10 mg/kg for period of 7 months also gave positive results by inhibiting the apoptosis in retina cells induced by higher glucose levels in diabetic patients (Soufi et al., 2012).

Diabetic Liver Damage

The main pathology behind the complication is liver fibrosis, inflammation of liver called steatohepatitis, and infiltration of intrahepatic fatty tissue. The improper treatment can lead this complication to liver cirrhosis or liver cancer. The recent study gave results that by administering 20 or 40 mg/kg of resveratrol orally inhibits the activation of NF- κ B pathway and other inflammatory mediators, which results in the low chances of liver damage. Moreover, another study shows that resveratrol in 10 mg/kg dose for 15 days reduces both blood glucose level and chances of liver damage by reducing the oxidative stress (Hamadi et al., 2012).

5.2. Potential of Phytoalexins in Treatment of Various Types of Cancer

According to the data, cancer is seeming to be a threat and a worldwide killer. It accounts for about 23% of the total deaths in USA and is the second most common disease after cardiac diseases. Cancer is the abnormal growth of cells which is caused by both internal and environmental factors like diet, stress, etc.

The phytoalexins like resveratrol, and others shows the anti-cancer effects and can be used in the cancer therapy. The phytoalexins inhibit the S and G₂ phase of cell cycle and efficiently causes apoptosis in many types of cancer like leukemia, colon cancer, prostate cancer and breast cancer (Rauf et al., 2018).

Anticancer Potential of Phytoalexins in:

Skin Cancer

Brassinin, an indole phytoalexin which was first found as a main constituent of cabbage has been shown to have

anticancer properties. Later, it was synthesised and found to be effective against the cancer. The phytoalexin was effective against the skin tumor. The activity was observed in 90 day study when the agent was injected in the mice and gave positive results without any side effects and toxicity. The mechanism of action of brassinin is unclear but the unique structural characteristics of the compound of having indole nucleus and isothiocyanate-based side chain, gives great anticancer activity (Mehta, 1995).

Breast Cancer

It is the major health problem in women in both developing and developed countries. There are more than one million breast cancer cases diagnosed each year. Resveratrol inhibits the breast cancer by various mechanisms such as it decreases the release of anti-apoptotic proteins like NF κ B, it suppresses the cell growth by inducing apoptosis. Moreover, it decreases the gene expression of BCL-xl in HER-2 receptor positive and negative breast cancer cell lines (Abdel-Latif, 2015).

Stomach Cancer

In order to treat stomach cancer, the phytoalexin (resveratrol) lowers the mRNA expression of BCL-2, stimulates cytochrome C and caspase oxidase activities, and causes cell cycle arrest in G₀/G₁ phase (Mohapatra et al., 2014).

Brain Cancer

Brain cancer is found to be a untreated problem from years. The number of patients of brain tumour have reached 43,800 per year in US. Currently 12,690 patients have died due to this disease. Resveratrol which is effective against many cancer, is also used in the therapy of brain cancer. The phytoalexin crosses the blood brain barrier and reduces the oxidative stress, inflammation and induces apoptosis. Moreover, resveratrol also activates p53, NF- B, Wnt, m-TOR etc. to influence the cancer cell death. Now, resveratrol is used as clinical therapy and saving lives of cancer patients effectively (Riles, 2006).

Lung Cancer

Lung cancer incidents are now increasing worldwide. Exposure to dust particles or respiratory diseases can lead to this highly prevalent disease. The phytoalexins are found to be effective against lung cancer as they work by various mechanisms, it suppresses the XRCC1 gene and also shows synergistic effect with etoposide (Kiskova, 2020). It also inhibits blocks the proliferation of H838 and H520 cells. It also inhibits the endothelial growth factor and AKT/ m-TOR mediated pathways (Wang et al., 2015).

3.3. Potential of Phytoalexin in Treatment of Neurodegenerative Diseases

Neurons are the building blocks of the nervous system. The degeneration and ageing of neurons due to any of mechanism whether increase in oxidative stress or other lead to death of nerve cells and cause various diseases like alzheimer's, parkinson's disease, huntington's disease and many more (Chen et al., 2015).

Potential of Phytoalexins in Brain Damage

The preclinical studies gave results that administration of phytoalexin intraperitoneally improves the motor and cognitive impairment and reduces the nerve cell death and damage. Therefore, can be beneficial in the treatment of many CNS disorders marked by nerve cell damage. For example, it showed positive results in treatment of seizures induced by ferric chloride, kainic acid etc. Phytoalexins also shows antioxidant properties as resveratrol protects nerve cells by activating the sirtuin proteins (Pallàs et al., 2009).

Alzheimer's Disease

Alzheimer's disease also called dementia is a progressive neurodegenerative disease as it damages the memory and cognitive functioning. The formation of β -amyloid plaques is the main pathogenesis behind it. The resveratrol is involved in the degradation and inhibition of polymerization of peptide by activating the proteasome. It also act by increasing the free radical scavenger glutathione and decrease the activity of acetylcholinesterase enzyme. As inflammation also contributes to this disease, so activation of SIRT1 (sirtuin1) and inhibition of inflammatory mediators by resveratrol give positive results in the treatment of the disease (Pallàs et al., 2009; Chen et al., 2015).

Parkinson's Disease

It is neurodegenerative disease characterized by nerve cell damage and causes low levels of dopamine, showing symptoms like stiffness, tremors and rigidity in movement. According to various in-vitro and preclinical studies it was concluded that resveratrol shows positive results in the treatment by activating proteins SIRT1 and SIRT2 as the activation shows antioxidant effects (Rocha-González, Ambriz-Tututi & Granados-Soto, 2008).

Epilepsy

It is a CNS neurodegenerative disease caused by nerve cell damage and disturbance leading to episodes of unusual behavior called as seizures or convulsions. Just like other anti-seizure drugs resveratrol also acts by inhibiting the

high voltage Na⁺ channels and shows anticonvulsant action (Chen et al., 2015).

Huntington's Disease

It is the inherited CNS condition in which the nerve cells break down resulting into symptoms like depression, loss in concentration, mood swings and aggressive behavior. Resveratrol acts as antioxidant, protects the nerve cell damage by activating sirtuin proteins SIRT1 and SIRT2. The results of preclinical studies on rats showed that administration of resveratrol in dose of 5-10 mg/kg improves the motor movement and cognitive impairment (Rocha-González, Ambriz-Tututi & Granados-Soto, 2008).

Conclusion

Plants are prone to diseases, in response to that they release chemicals known as phytoalexins or antimicrobial compounds. Phytoalexins, synthesised by plants in response to pathogenic diseases and microbial infections, show great importance in human health. They contribute in the treatment and prevention of various life threatening diseases like diabetes mellitus, cancer, brain damage, and heart attack. The phytoalexins treat most of the diseases because of having anti-inflammatory and anti-oxidative properties. Decrease in oxidative stress leads to the management and control of diseases. Thus, the review holds the current applications of phytoalexin in human health and diseases.

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Authorship Contribution

Bhavika Arora: Data Collection;

Rakesh K Sindhu: Manuscript Design and evaluation;

Sandeep Arora: Manuscript evaluation.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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