

# Phytoalexins: Current and possible future applications in human health and diseases control

## Abstract

Plants are prone to diseases and infections following their obvious exposure to microbes and attendant microbial attacks. Plants control diseases and infections by using their secondary metabolites known collectively as phytoalexins. These phytoalexins, usually synthesized in plants in response to diseases and infections, have enormous chemical diversity and biologic roles but are essentially non biodegradable owing to their stable structures hence could bio-accumulate with sustained effect once synthesized. Thus, this reviewed current and possible future applications of phytoalexins in human health and diseases control using relevant search words and search engines. The review noted that resveratrol, a representative of, and an extensively studied, phytoalexins was variously implicated in the management of human health, including in the prevention of cardiovascular disease and cancers. Resveratrol acts via mechanisms essentially related to its capacity to ameliorate oxidative stress perhaps by significantly enhancing the synthesis of nitric oxide, NO, which could act as an antioxidant. Increased oxidative stress has been implicated in human diseases and efforts aimed at mitigating (or preventing the onset of) oxidative stress have been the underlying approach to human disease management and control. Thus, the current applications of phytoalexins as shown by resveratrol could be extended to other human health and diseases, warranting detailed empirical studies.

**Keywords:** phytoalexins, resveratrol, bioaccumulation, cardio-protective, cardio-mycetes

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**Abbreviations:** MRSA, methicillin-resistant *Staphylococcus aureus*; LPS, lipopolysaccharide; TNF- $\alpha$ , tumor necrotic factor-alpha; NO, nitric oxide; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate.

## Introduction

Plants are prone to diseases and infections following their obvious exposure to microbes and attendant microbial attacks. Plants, therefore, accumulate an armory of anti microbial secondary metabolites which they use for protection against pathogenic microorganisms and for controlling resultant diseases and infections. Those anti microbial secondary metabolites are known collectively as phytoalexins. Phytoalexins are antimicrobial compounds.<sup>1</sup> Phytoalexins are a group of photochemical of low molecular weight which inhibit microorganisms and accumulate in plants following interaction of the plant with microorganisms.<sup>2</sup> The production of phytoalexins in the plant once the pathogen has been detected involves induced response mechanism resulting in the secretion of the antimicrobial compounds to the infected sites.<sup>3</sup> Thus, phytoalexins can aside acting as plant, could act as human, disease controlling antimicrobial agents. For example, hydroxycoumarin scopoletin (6-methoxy-7-hydroxycoumarin), a major phytoalexins in tobacco plants, displays antimicrobial activity.<sup>4-6</sup> It elicited scavenging activity over reactive oxygen specie.<sup>7</sup> They are essentially non biodegradable owing to their stable structures hence could bio-accumulate with sustained effect once synthesized. Thus, plants have always been good direct and indirect sources of drugs, including many of the currently available drugs. For instance, a wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possi-

ble use in the treatment of diabetes mellitus.<sup>8</sup> Many plant associated microbes are pathogens that affect plant overall physiology and health status of living things. Phytoalexins represent constitutive chemical barriers to microbial attacks which are usually activated either prior to or on recognition of pathogen elicitors.<sup>9</sup> Thus, this reviewed current and possible future applications of phytoalexins in human health and diseases control.

The chemical diversity and biologic roles of phytoalexins are enormous. The diversity perhaps derives from their varied plant sources. Thus, to achieve the review aim, resveratrol - a representative of, and an extensively studied, phytoalexins was studied. Resveratrol was variously implicated in the management of human health, including in the prevention of cardiovascular disease and cancers. Resveratrol acts *via* mechanisms essentially related to its capacity to ameliorate oxidative stress perhaps by significantly enhancing the synthesis of nitric oxide, NO, which could act as an antioxidant. Increased oxidative stress has been implicated in human diseases and efforts aimed at mitigating (or preventing the onset of) oxidative stress have been the underlying approach to human disease management and control. This review could provide update on the current applications of phytoalexins as shown by resveratrol and in addition provide deep insight on possible future application of phytoalexins in human health and diseases control that could provoke detailed empirical studies.

## Methods

In this review, conventional search engines, including Google and relevant search words were used. In particular, current and possible future applications of phytoalexins in human health and diseases control were highlighted.

Current and possible future applications of Phytoalexins in human health and diseases control

### Phytoalexins as antimicrobial agents

Phytoalexins are antimicrobials<sup>1</sup> and accumulate in plants to inhibit microorganisms following interaction of the plant with pathogenic microorganisms.<sup>2</sup> Phytoalexins production by plants following detection of pathogens (an induced response mechanism) results in the secretion of the potent antimicrobials to the infected sites.<sup>3</sup> The antimicrobial potentials of phytoalexins could be exploited in managing human diseases caused by microbes. For example, Hydroxycoumarin scopoletin (6-methoxy-7-hydroxycoumarin), which represents major phytoalexins in tobacco plants, elicited antimicrobial activity<sup>4-6</sup> and in rats even improved serum bio-indicators of varied organs functions in rats.<sup>10-12</sup> Currently, phytoalexins are utilized as antibiotic potentiators.<sup>13,14</sup> A good example is epigallocatechin-gallate which potentiated the activity of  $\beta$ -lactam antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) by mechanisms involving binding of the catechin in the bacterial wall.<sup>15</sup> Phytoalexins from garlic extract and from cranberry fruit exhibited antimicrobial properties against many pathogens.<sup>16</sup> Other antimicrobial activities mediated by various phytoalexins have been documented.<sup>17-19</sup>

### Phytoalexin as anti inflammatory, antitumor and anticancer agents

Phytoalexins act as anti-inflammatory agent via poorly characterized mechanism that involves the prevention of the expression of inducible nitric oxide synthases (NOS) which is involved in the production of a high concentration of NO by inducible NOS in inflammation.<sup>20</sup> Resveratrol, the most studied phytoalexins, inhibited the inflammatory response of even colon cancer cell lines induced by lip polysaccharide (LPS) by inhibiting the signaling pathway possibly related to a direct action on the nuclear transcription factor *via* phosphorylation inhibition<sup>21</sup> or by reversal of the level and expression of, for instance, hepatic tumor necrotic factor-alpha, TNF- $\alpha$ .<sup>22,23</sup> Cancer is a multistep disease characterized by uncontrolled cell growth, acquisition of metastatic properties and complex communications between intricate signaling networks.<sup>24,25</sup> Phytoalexins could suppress tumor progression to cancer since inflammation-mediated processes, including the production of cytokines, chemokines, and reactive oxygen and nitrogen species may contribute to malignant cell transformation.<sup>26,27</sup> In essence, phytoalexins could control the initiation and progression of cancer by way of their anti-inflammatory activities. Resveratrol inhibited the inflammatory response of colon cancer cell lines.<sup>21</sup> Synthesized substituted resveratrol analogs exhibited more potent anti-tumor and anti-inflammatory effects.<sup>28</sup>

### Phytoalexin as anti hyperglycemic agent

The patho-physiological mechanisms leading to hyperglycemia and eventually to diabetes involve an inappropriate secretion of insulin or insulin resistance or both.<sup>29</sup> Hyperglycemia can result to or from reduced number of glucose transporters, down regulation in the number of insulin receptors as well as defects of tissue insulin signal transduction. And, eventually to absolute increase in hepatic glucose output exceeding glucose utilization and protein wasting due to the unavailability of carbohydrates for energy metabolism.<sup>30,31</sup> These series of metabolic events were improved following resveratrol exposure to diabetic rats, suggesting that resveratrol could induce blood glucose homeostasis to prevent hyperglycemia.<sup>32</sup> Persistent

hyperglycemia resulting in glycation of hemoglobin (formation of glycosylated hemoglobin) hence decreased level of hemoglobin in diabetic patients was restored, though in diabetic rats treated with resveratrol and glyclazide for 30 days.<sup>33</sup>

### Phytoalexin as anti-apoptotic and cardio protective agents

Increased myocardial cell apoptosis,<sup>34</sup> mitochondrial dysfunction<sup>35</sup> and caspase-independent apoptosis pathway<sup>36</sup> were involved in the mediation of cardio-toxicity. Evidence abound that resveratrol could act as an anti-apoptotic agent to provide cardio-protection through inhibition of caspase-3 expression and activity.<sup>37,38</sup> Previous study showed that cardiotoxic effects of injection of doxorubicin, a cardio-toxic agent, were ameliorated on concomitant administration/injection with resveratrol.<sup>35,39-41</sup> The apparent benefit of resveratrol in the prevention of cardiovascular disease<sup>41</sup> as well as other significant health conditions including protection against cancers,<sup>42</sup> obesity, diabetes,<sup>43</sup> neurodegenerative diseases<sup>44</sup> supports important future applications of phytoalexins in human diseases control.

### Phytoalexin in oxidative stress

Interestingly, chronic administration of resveratrol protected a variety of tissues against ischemic injury by reducing the free radical production.<sup>45,46</sup> The reduction of free radicals by resveratrol could protect neurons which are vulnerable to the reactive oxygen species generated by ischemia-reperfusion.<sup>47,48</sup> Resveratrol administration in rats significantly increased the hippocampal NO (nitric oxide) production resulting to increased cerebral blood flow to protect animal from ischemia-induced neuron loss.<sup>49</sup> Nitric oxide is a vascular dilator, hence could on dilation of the arterial wall increase the arterial volume while reducing the arterial pressure based on the Boyle's law. Evidence abound suggesting that increased oxidative stress with increased free radical production and decreased myocardial endogenous antioxidants play an important role in the pathogenesis of cardio-toxicity.<sup>50-52</sup> Phytoalexins elicited scavenging activity over reactive oxygen species.<sup>7</sup> Resveratrol treatment prevented the severity of doxorubicin-induced cardio-toxicity by alleviating the extent of oxidative stress<sup>50</sup> as demonstrated by increased levels of superoxide dismutase (SOD) and decreased levels of malondialdehyde.<sup>37</sup> Possible mechanisms for resveratrol-induced antioxidant activities have been elucidated and involve among others the reduction of basal ROS (reactive oxygen species) generation, subsequent polarization of mitochondrial membrane potential<sup>52,53</sup> and by inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) or attenuating cellular oxidative stress.<sup>54</sup> The possible application of phytoalexins, notably resveratrol in combating oxidative stress is will have significant impact in human diseases and control as oxidative stress is fundamental to many diseased conditions.<sup>55-57</sup> Thus detailed research studies in this area are warranted and recommended. Further evidence abound that the most studied phytoalexins, resveratrol (3,5,4'-trihydroxystilbene), interacted with molecular targets affecting apoptosis, including protein kinases and transcription factors to increase apoptosis<sup>58-62</sup> and, possible mechanisms of resveratrol actions have been documented including prevention of mutagenesis and even inhibition of DNA synthesis.<sup>63-71</sup>

### Chemical diversity of phytoalexins

Phytoalexins are not restricted to resveratrol. Diverse chemically active phytoalexins exist that belong to various families, including

phenolics, terpenoids, furanoacetylenes, steroid glycoalkaloids, indoles,<sup>72-74</sup> and as resveratrol, have wide application in human health and disease. The chemical diversity of phytoalexins, their plant family source (and reported role in human health and diseases) are as surmised in (Table 1).<sup>72,75-78</sup>

**Table 1** Phytoalexins from different plant families and some reported role(s) in human health and diseases<sup>72,75-78</sup>

| S/N | Phytoalexins   | Plant family         | Role(s) in human health and diseases   |
|-----|--|----------------------|--|
| 1   | Resveratrol (Stilbenes)  | Vitaceae (grapevine) | anti-oxidant, anti carcinogenic/antiproliferative agent exerting antitumor activity either as a cytostatic or a cytotoxic agent in various cancers |
| 2   | Flavans  | Amaryllidaceae       | -  |
| 3   | Camalexin (Indole); Brassinin (sulphur containing)   | Brassicaceae         | antiproliferative activities in human colorectal cancer cells in vitro, Induction of apoptosis in prostate cancer cells                            |
| 4   | Betagarin (Flavanones); betavulgarin (Isoflavones) Safynol (Polyacetylenes)  | Chenopodiaceae       | -  |
| 6   | Casbene (Diterpenes)   | Euphorbiaceae        | -  |
| 7   | Ipomeamarone (Furanosesquit-erpenes)   | Convolvulaceae       | -  |
| 8   | Terpenoids; gossypol (naphthaldehydes)   | Malvaceae            | -  |
| 9   | Isoflavones; Isoflavanones; Coumestans (Isoflavans)  | Leguminosae          | -  |
| 10  | Momilactones (Diterpenoids); Oryzalexins; Zealexins; Phytocassanes; Kauralexins; Apigeninidin; Phenylamides Luteolinidin (Deoxyanthocyanidins); Sakuranetin (Flavanones) | Poaceae              | -  |
| 11  | Moracins A-H (Furanopterocarpanes)   | Moraceae             | -  |
| 12  | Loroglossol (Dihydrophenanthrenes)   | Orchidaceae          | -  |
| 13  | Xanthoxylin (Methylated phenolic compounds)  | Rutaceae             | -  |
| 14  | Falcarinol (Polyacetylenes); Xanthotoxin (Phenolics); 6-methoxymellein   | Apiaceae             | -  |
| 15  | Auarperin (Biphenyls) Cotonefurans (Dibenzofurans)   | Rosaceae             | -  |
| 16  | Phenylpropanoid related compounds; Steroid glycoalkaloids ; Norsequi and sesquiterpenoids; Coumarins; Polyacetylenic derivatives   | Solanaceae           | -  |
| 17  | Maslinic acid (Triterpene)   | Olives               | Antitumor, antidiabetic, neuroprotective, cardioprotective, antiparasitic and growth -stimulating agent  |
| 18  | 3- deoxyanthocyanidins (flavonoid phytoalexins)  | Poaceae              | Reduction of incidence of gastro-intestinal cancer   |
| 19  | Indoles and stilbenes  | -                    | Cardioprotective activity  |
| 20  | Steroid glycoalkaloids   | potato               | Varied level of toxicity in humans   |
| 21  | Dimeric sesquiterpene gossypol   | cotton               | Varied level of toxicity in humans   |

## Conclusion

Phytoalexins are essentially non biodegradable owing to their stable structures hence could bio-accumulate with sustained effect once synthesized. Phytoalexins synthesized and usually released by plants in response to diseases and infections have ameliorative potential on diabetes mellitus, ischemia, cardiomyocytes apoptosis, cancer, tumor, microbial pathogens, hyperglycemia and oxidative stress, hence could be beneficial in human diseases control. These effects were enormous owing to the chemical diversity of phytoalexins from varied plant sources and were in this review substantiated using resveratrol, a representative of, and an extensively studied, phytoalexins via mechanisms essentially related to their capacity to ameliorate oxidative stress that involve among other enhancing the synthesis of nitric oxide, NO, which could act as an antioxidant and as a vascular dilator. In particular, increased oxidative stress has been implicated in human diseases and efforts aimed at mitigating (or preventing the onset of) oxidative stress have been the underlying

approach to human disease management and control. Thus, the current applications of phytoalexins as shown by resveratrol could be extended to other human health and diseases, warranting detailed empirical studies.

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## Conflict of interest

The author declares no conflict of interest.

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