Phytoantibiotics – Antibiotics Sourced from Plants

- By Divya Narayan (I am a post-graduate in Biochemistry from the University of Mumbai)

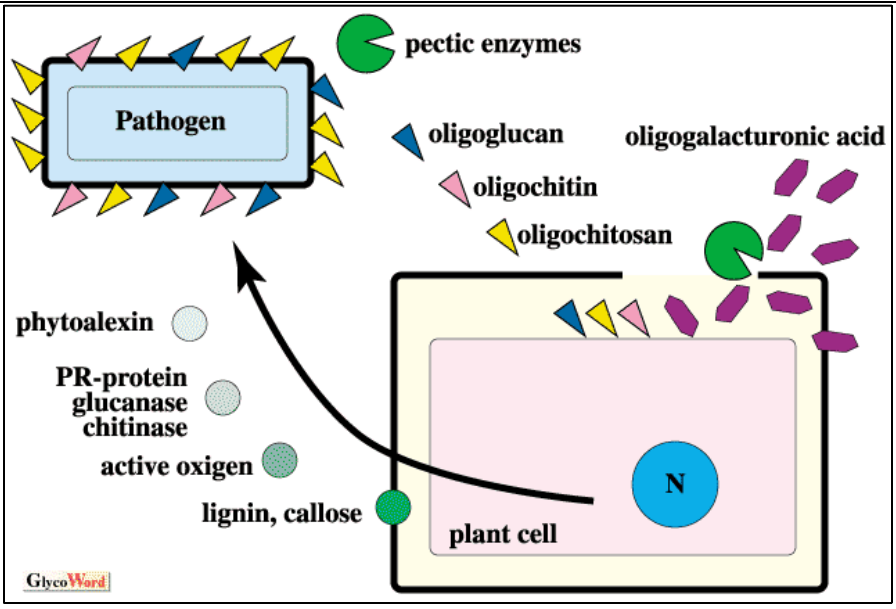
Summary:
Conventional antibiotics have resulted in drug resistance due to rampant consumption as well as giving rise to side-effects. Phytoantibiotics or plant antibiotics can be regarded as a suitable alternative for therapeutic purposes.

What are phytoantibiotics?
Antibiotics sourced from plants are known as phytoantibiotics. These can be regarded as an alternative source of antibiotics as compared to the more commonly occurring fungi, as well as synthetically-produced antibiotics. Plant antibiotics are also known as plant defensins.

Need for Plant antibiotics
Antibiotics are often described as the wonder drugs of the 20th century. However, increasing and rampant use of these antibiotics have resulted in antibiotic resistance. Additionally, these antibiotics produce numerous side-effects such as gastrointestinal disorders, allergies, etc. [1]
It is hoped that plant-sourced and plant-based antibiotics would help in negating these side-effects as well as prove to be an effective form of resistance to infection [2] (preventive therapy).

Types of Phytoantibiotics
Phytoantibiotics occur in two forms –
Phytoalexins - The term 'phytoalexin' was coined by K.O. Muller to imply those antibiotics produced by plants after exposure to infection from external sources. [3] In other words, phytoalexins can be regarded to be produced when they satisfy the following criteria –

- External elicitation / exposure from bacteria resulting in infection
- Occurrence of plant metabolic activity so as to produce the antibiotic product
- No preformed products prior to exposure
- Rapid accumulation in infected tissue
- Forming basis of disease resistance
- Suppression of phytoalexin synthesis results in susceptibility to infection [1,3]



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Phytoanticipins – The term 'Phytoanticipins' was proposed by Mansfield. These phytoantibiotics are present inside the plant source prior to any kind of exposure to bacterial infection hence preformed. [1] Phytoanticipins can also be regarded to be produced after exposure to infection provided the precursors of said products are preformed and present before exposure to infection. [1]

Based on the above definitions, the same plant antibiotic may be regarded as a phytoalexin as well as a phytoanticipin derived from the same source itself purely depending on *how* it is produced. [1]

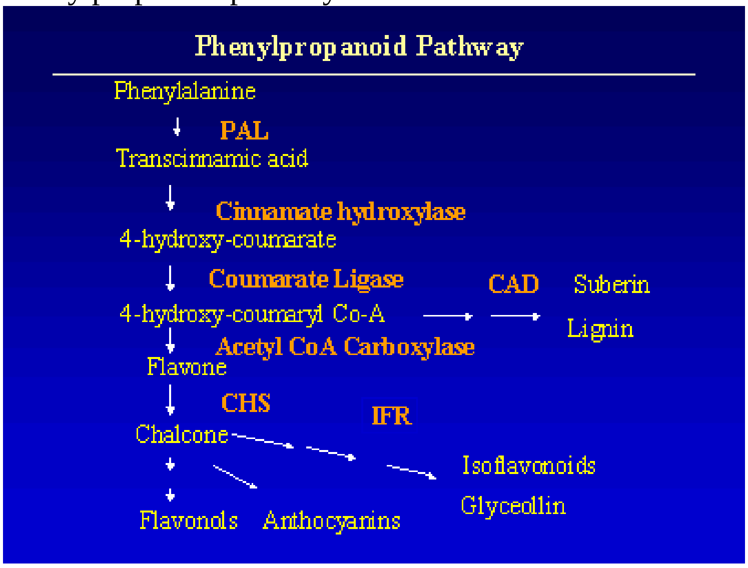
The understanding of this difference is extremely critical in understanding the mechanism of synthesis of the two types of phytoantibiotics.

Synthesis of phytoantibiotics

- Phytoalexin synthesis – It is mainly reported in dicotyledonous plants but has also been found to occur in monocotyledonous plants as well as gymnosperms. [5]

  There are two pathways used for the synthesis of phytoalexins -

  - Phenylpropanoid pathway [5]



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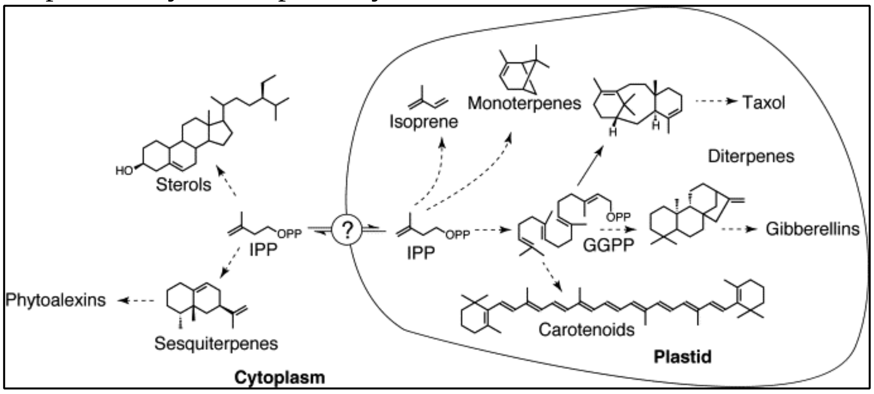
- Terpene biosynthetic pathway [5]



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Phytoalexins neutralize bacterial invasion as follows – [8]

- Puncturing of bacterial cell wall
- Delaying maturation of pathogen inside the plant cell
- Disruption of bacterial metabolism
- Prevention of bacterial reproduction

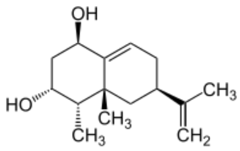
It has been observed that plants become increasingly susceptible to bacterial infection as a result of reduction in the production of phytoalexins. [3]

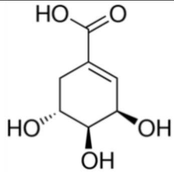
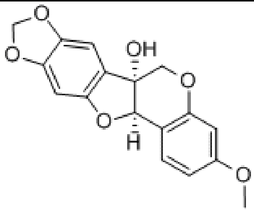
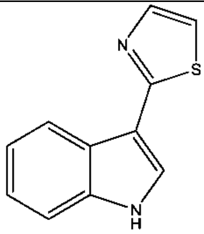
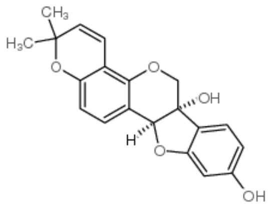
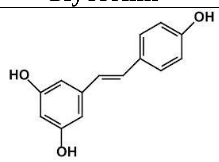
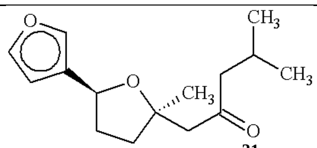
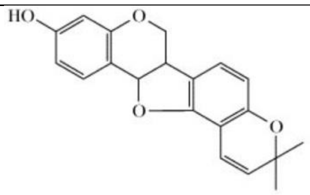
- <u>Phytoanticipin synthesis</u> – Phytoanticipins are present in plant source prior to exposure to any kind of bacterial infection. Hence these are naturally occurring in the plant body. As per some definitions, phytoanticipins can also be regarded as 'constitutive phytoalexins' as these compounds are naturally present and produced at a constant rate. [9]

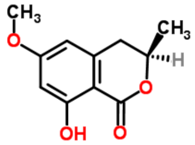
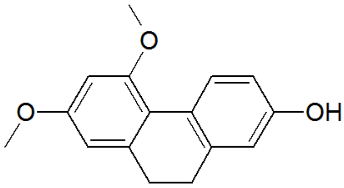
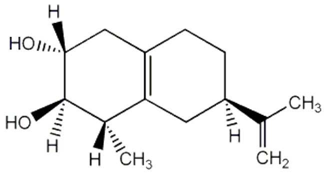
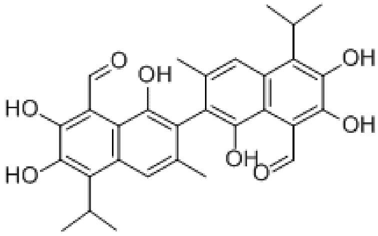
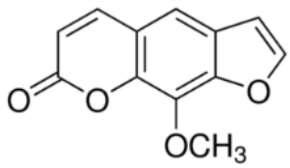
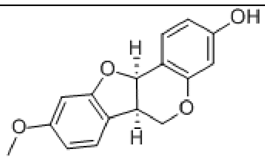
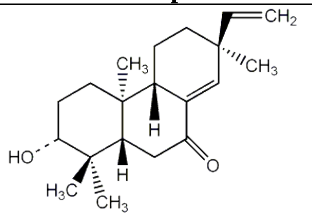
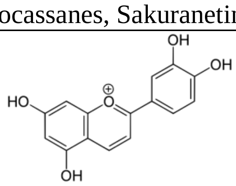
  Some phytoanticipins are present on the plant surface. Additionally, they occur as preformed precursors which are present in the vacuole. The conversion of these precursors into antibiotics as well as their release takes place after pathogenic infection due to the action of a hydrolyzing enzyme. The formation of this enzyme takes place in a similar manner post exposure to infection. [10]

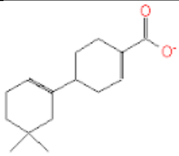
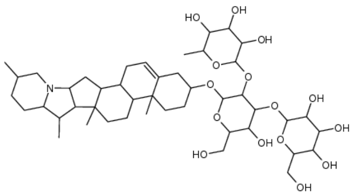
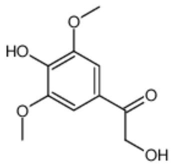
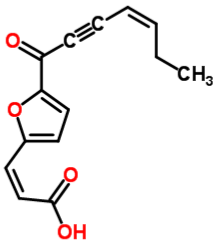
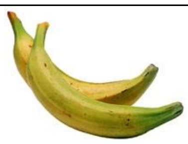
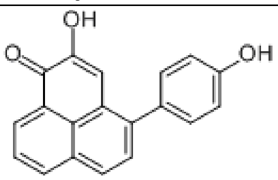
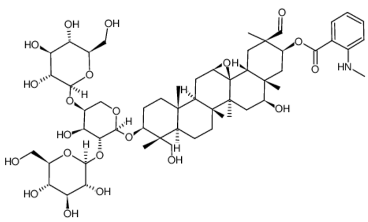
  Phytoanticipins possess antifungal activity and are chemically present in the form of glycosides, glucosinolates, and saponins. [11]

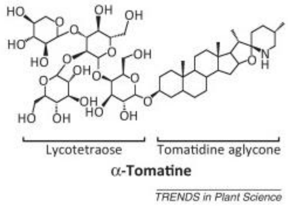
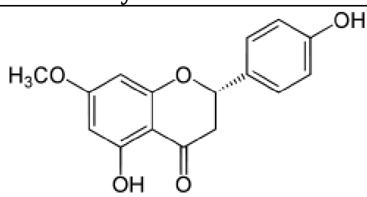
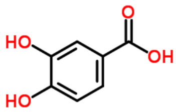
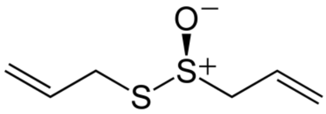
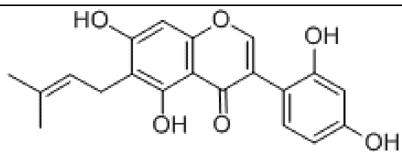
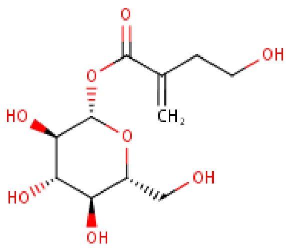
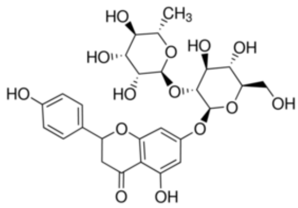
Examples of phytoantibiotics

Phytoalexins		
Source	**Antibiotic produced**	**Effect**
 **Chili pepper** [12] **(*Capsicum annuum*)**	 **Capsidiol** [13]	Displays antifungal activity and inhibits germination of spores in response to fungal infection in plants by *Phytophthora capsici* [14]

 **Pine needles of Deodar cedar (*Cedrus deodara*)** [15]	 **Shikimic acid** [16]	Antibacterial activity by damaging cell membrane of *Staphylococcus aureus* [17]
 **Garden pea (*Pisum sativum*)** [18]	 **Pisatin** [19]	Broad spectrum antibiotic stimulated by fungal growth, UV radiation, ethylene [20]
 **Thale cress (*Arabidopsis thaliana*)** [21]	 **Camalexin** [22]	Antifungal activity against *Sclerotinia sclerotiorum which causes white* mold *disease in Arabidopsis* [23]
 **Soybean (*Glycine max*)** [24]	 **Glyceollin** [25]	Produces anti-nematode activity against larvae of *Meloidogyne incognita*[26]
 **Red Grapes (*Vitis vinifera*)** [27]	 **Resveratrol** [28]	Antimicrobial activity against *Propionibacterium* in vitro and inhibition of *Escherichia coli* via reactive oxygen species [29]
 **Sweet potato (*Ipomoea batatas*)** [30]	 **Ipomeamarone** [31]	Antibiotic activity in black rot disease of sweet potato caused by the fungus *Ceratostomella fimbriata* [32]
 **French bean (*Phaseolus vulgaris*)** [33]	 **Phaseolin** (in fig.) (Phaseollidin, Phaseollinisoflavan, Kievitone, Coumesterol) [34,35]	Antifungal inhibitory effect observed in-vitro on *Penicillium roqueforti* DPPMAF1 as indicator fungus [36]

 **Carrot** **(*Daucus carota* subsp. *sativus*)** [37]	 **6-Methoxymellein** [38]	Broad spectrum antibiotic against fungi, yeasts, bacteria. Anti-fungal activity displayed in-vitro by cultured carrot cells. [39]
 **Military orchid** **(*Orchis militaris*)** [40]	 **Orchinol** [41]	Produced upon infection by *Rhizoctonia repens*. Antifungal activity [42]
 **Diseased potato** **(*Solanum tuberosum*)** [43]	 **Rishitin** [44]	Accumulation has an effect on the resistance of plants against potato late blight disease caused by *Phytophthora infestans* [45]
 **Tree Cotton** **(*Gossypium arboreum*)** [46]	 **Gossypol** [47]	Pronounced antibiotic activity and biochemical resistance towards the cotton spotted bollworm *Earias vittella* [48]
 **Parsnip** **(*Pastinaca sativa*)** [49]	 **Xanthotoxin** [50]	Inhibits specific P450 oxygenase activity in *Fusarium sporotrichoides* [51]
 **Chickpea** **(*Cicer arietinum*)** [52]	 **Medicarpin** [53]	Antifungal and antibacterial activity [54]
 **Rice** **(*Oryza sativa*)** [55]	 **Oryzalexins** (in fig.), Momilactone, Phytocassanes, Sakuranetin [56,57]	Mycelial growth of *Pyricularia oryzae* (causing blast or blight disease) was inhibited by the action of Oryzalexin D [58]
 **Great millet** **(*Sorghum bicolor*)** [59]	 **Luteolinidin** (in fig.),	Antioxidant activity as well as protective agent against anthracnose caused by the pathogenic fungus *Colletotrichum*

	Apigeninidin[60,61]	*sublineolum*[62]
 **Maize** **(*Zea mays* subsp. *mays*)** [63]	 **Zealexins** (in fig.), Kauralexin [64,65]	Inhibits the growth of *Aspergillus flavus*, *Fusarium graminearum*, and *Rhizopus microspores* [66]
 **Potato peels** **(*Solanum tuberosum*)** [67]	 **Alpha-solanine** (in fig.), alpha-chaconine [68,69]	Antibacterial activity against Gram positive *Streptococcus pyogenes* and *Staphylococcus aureus* [70]
 **Papaya** **(*Carica papaya*)** [71]	 **Danielone** [72]	High antifungal activity against the pathogen *Colletotrichum gloeosporioidies* [73]
 **Fava bean** **(*Vicia faba*)** [74]	 **Wyerone Acid** [75]	Inhibits mycelial growth of the fungus *Botrytis cinerea* causing gray mold disease [76]
 **Plantain** **(*Musa x paradisiaca*)** [77]	 **Irenolone** (in fig.), Emenolone[78,79]	Shows antimicrobial activity against *Colletotrichum musae* and *Mycospherella fijiensis* [80,81]
Phytoanticipins		
Source	**Antibiotic produced**	**Effect**
 **Oat roots** **(*Avena sativa*)**[82]	 **Avenacin A-1** [83]	Effective as antibiotic in roots and displays antifungal properties against *Gaeumannomyces graminis* [84]

 **Tomato** (***Solanum lycopersicum***) [85]	 **Tomatine, Tomatidine, Lycotetraose** [86]	Tomatidine inhibits replication of *Staphylococcus aureus* [87]
 **Black currant** (***Ribes nigrum***) [88]	 **Sakuranetin** [89]	Possesses fungicidal action (present as a phytoalexin in rice, but as a phytoanticipin in black currants) [66]
 **Dried flowers of Roselle** (***Hibiscus sabdariffa***) [90]	 **Protocatechuic acid** [91,92]	Induces apoptosis in in-vitro cell models [93]
 **Garlic** (***Allium sativum***) [94]	 **Allicin** [95]	Anti-bacterial action against drug resistant strains of *Escherichia coli*, anti-fungal, anti-viral, anti-parasitic activity [96]
 **Common labarnum** (***Laburnum anagyroides***) [97]	 **Luteone** (in fig.), Wighteone [98,99]	Antibacterial activity against sensitive and resistant strains of *Staphylococcus aureus* [100]
 **Tulip** (***Tulipa gesneriana***) [101]	 **Tuliposides** [102]	Antifungal activity, contributes to resistance to the fungus *Botrytis tulipae*, anti-microbial activity [103]
 **Dried peel of Grapefruit** (***Citrus x paradisi***) [104]	 **Naringin** (in fig.), Tangeretin [105,106]	Anti-inflammatory and antioxidant activities. Studies have proved the beneficial effects of naringin against metabolic disorders [107]

Regulation of phytoantibiotic production

Phytoantibiotics are also known as plant defensins.

- Phytoalexins – Phytoalexins are produced only after exposure to pathogens. So, the following regulate its production – [108]

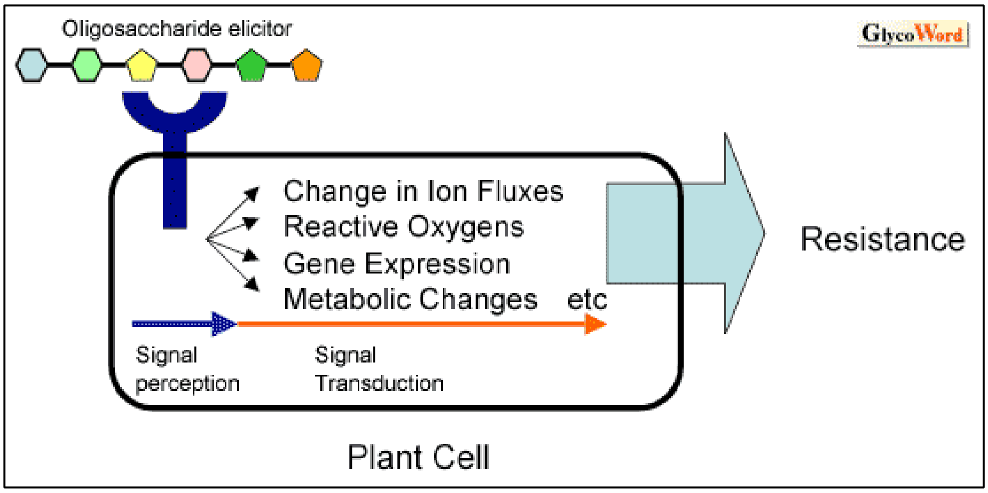
  ➢ If the host plant is under no physical, chemical (accumulation of toxins), or biological stress (bacterial infection), production of phytoalexins does not take place.

  ➢ Phytoalexin production increases as a result of (1) Introduction of synthetically modified phytoalexin genes inducing antibiotic production, (2) Introduction of synthetically produced toxins which elicit antibiotic production, (3) Exposure of the plant to biotic and abiotic stress.

  ➢ Phytoalexin production decreases due to (1) Presence of phytoalexin inhibitor in pathogen, (2) Chemical treatment affecting antibiotic production, (3) Production of antibiotic inhibitor inside host, (4) Failure of transcription leading to lack of phytoalexin producing enzymes, (5) Pathogen produces enzyme neutralizing toxicity of antibiotic.

  Biotic elictor of phytoalexin – Interaction between host plant and pathogen [109]

  Abiotic elicitor of phytoalexin – Fungicides, salts of heavy metals, detergents, intercalated DNA [109]



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  Enzymes involved in regulation of phytoalexin synthesis are Mitogen-affected Protein Kinase involving (MPK3 and MPK6). The transcription factor WRKY33 is direct target of MPK3 and MPK6 signalling. Camalexin production in Arabidopsis is brought about by phosphorylation of WRKY33 (action of MPK3/MPK6). [111]

- Phytoanticipins – Phytoanticipins are preformed antibiotics present in plants, produced before exposure to infection. Hence their production is not regulated by any conditions.

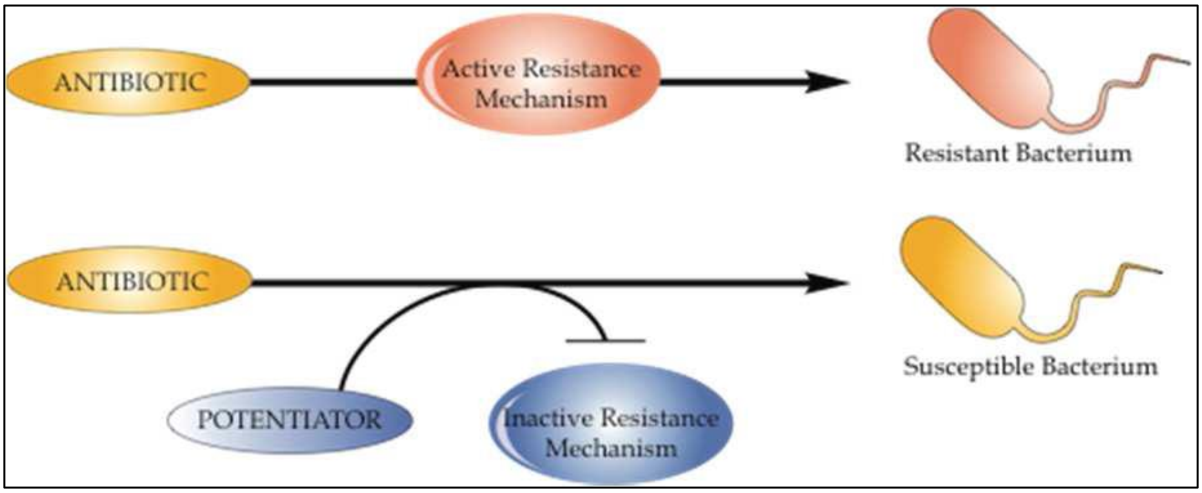
Phytoantibiotics for human therapy

The main purposes of employing phytoantibiotics for human therapeutics are the following – (1) Increasing instances of nosocomial infections, affecting community immunity, and (2) Acquiring of multi-drug resistance by pathogens due to limited variations in the existing antibiotic therapy available. Additionally, there is now greater acceptance for plant-based and naturally occurring therapeutics as compared to synthetic chemotherapeutics, partly due to lesser side effects. [112]

The main challenges in employing phytoantibiotics for human therapy are the difficulties encountered in separating active components present in plant sources which possess antibiotic properties. Additionally, pathogenic bacteria causing infections in humans are Gram negative organisms and phytoantibiotics show an extremely level of activity against them. On the other hand, Gram positive organisms have been found to be susceptible to the effects of these antibiotics. Fungi causing pathogenic infections can produce certain toxins which inhibit or negate the antibiotic activity of these phytocompounds. [112]

Despite the above mentioned challenges, phytoalexins and phytoanticipins can be used as "antibiotic potentiators" or "antibiotic adjuvants" in combination with conventional antibiotics so as to counter the limited range of medical arsenal against bacterial pathogens. For instance, tannic acid (98%) can be used in combination with the antibiotic fusidic acid (98%) against strains of MRSA (Methicillin Resistant *Staphylococcus aureus*). Beta-lactam antibiotics can be combined with ethyl gallate. [113] Tomatidine (derived from tomatoes) acts in combination with aminoglycoside antibiotics against antibiotic resistant *S. aureus*. [87]

Antibiotic potentiators work by – (1) Inhibition of elements promoting antibiotic resistance in pathogens, (2) Increasing antibiotic uptake by pathogen by increasing membrane permeability, (3) Blocking of those channels which might "throw out" antibiotics from the pathogens (efflux), (4) Modifications in pathogens affecting their functioning. [114]



Concept of drug potentiation by targeting resistance. An active resistance mechanism allows survival of bacterial pathogens in the face of an antibiotic(s). A potentiator that inhibits the resistance mechanism would (re)sensitize the bacteria to the antibiotic(s), thus enhancing antibacterial activity. [115]

Conclusion

Phytoantibiotics or plant antibiotics are a suitable means to carry out drug development. They possess the ability to fulfill the limitations imposed as a result of rampant and unchecked consumption of conventional antibiotics, resulting in multidrug resistance. These antibiotics have the added advantage of being sourced from natural environments hence resulting in minimal side-effects. However, the effect of these plant antibiotics on human cells is yet to be explored fully.

References (if any)

1. VanHatten HD, Mansfield JW, Bailey JA, Farmer EE. Two Classes of Plant Antibiotics:

Phytoalexins versus "Phytoanticipins". *Letters to the Editor, The Plant Cell*. 1994:1191-2.
2. Veech JA. Phytoalexins and their Role in the Resistance of Plants to Nematodes. *Journal of Nematology*. 1982;14(1):2-9.
3. Huang J-S. *Plant Pathogenesis and Resistance – Biochemistry and Physiology of Plant Microbe Interactions.* Springer-Science+Business Media, B.V (Dordrecht). Originally published by Kluwer Academic Publishers. 2001:590-600.
4. Ito Y. Oligosaccharide Elicitor Signaling in Plant-Pathogen Interactions. 1999. Available from http://www.glycoforum.gr.jp/science/word/saccharide/SA-A01E.html (Accessed on May 17, 2016)
5. Hestrella-Herrera L, Rosales LS, Rivera-Bustamante R. *Transgenic Plants for Disease Control.* In: Stacey G, Keen NT edn. *Plant Microbe Interactions.* Chapman & Hall, New York. 1996;1:33-80.
6. Secondary products | Soybean Genome Home. Available from http://bldg6.arsusda.gov/benlab/Soybean%20Defense%20Response/secondary_products.htm (Accessed on May 17, 2016)
7. McCaskill D, Croteau R. Some caveats for bioengineering terpenoid metabolism in plants. *Trends in Biotechnology*. 1998;16(8):349-355. doi:10.1016/s0167-7799(98)01231-1
8. Phytoalexin – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Phytoalexin#Function (Accessed on May 15, 2016)
9. Plant Pathology Glossary. Available from http://bugs.bio.usyd.edu.au/learning/resources/PlantPathology/glossary.html#Pwords (Accessed on May 15, 2016)
10. Hatsugai N, Hara-Nishimura I. Two vacuole-mediated defense strategies in plants. *Plant Signaling & Behavior*. 2010;5(12):1568-1570. doi:10.4161/psb.5.12.13319.
11. Pandey AK, Kumar S. Perspective on Plant Products as Antimicrobials Agents: A Review. *Pharmacologia.* 2013;4:469-480. doi: 10.5567/pharmacologia.2013.469.480
12. Chile Pepper | New Mexico Federation of republican Women. Available from http://nmfrw.com/chile-pepper/ (Accessed on May 16, 2016)
13. Capsidiol – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Capsidiol (Accessed on May 16, 2016)
14. Egea C, Alcázar MD, Candela ME. Capsidiol: Its role in the resistance of *Capsicum annuum* to *Phytophthora capsici*. *Physiologia Plantarum*. 1996;98:737–742. doi: 10.1111/j.1399-3054.1996.tb06679.x
15. Cedrus Deodara oil is antiseptic and used in skin diseases, sores, wounds, and ulcers. Available from http://www.doctorayur.com/index.php?option=com_content&id=98:cedrus-deodara- (Accessed on May 16, 2016)
16. SHIKIMIC ACID. (n.d.). Available from http://www.mpbio.com/product.php?pid=02152058 (Accessed on May 16, 2016)
17. Bai J, Wu Y, et al. Antibacterial Activity of Shikimic Acid from Pine Needles of *Cedrus deodara* against *Staphylococcus aureus* through Damage to Cell Membrane. In: Srivastava SK, ed. *International Journal of Molecular Sciences*. 2015;16(11):27145-27155. doi:10.3390/ijms161126015.
18. *Pisum sativum* Peptide, Pea Protein, Pea Peptide. Available from http://www.formulatorsampleshop.com/FSS-Pisum-Sativim-Peptide-p/fss16810.htm (Accessed on May 16, 2016)
19. Pisatin 20186-22-5 | Chemical Book. Available from http://www.chemicalbook.com/ChemicalProductProperty_EN_CB41366484.htm (Accessed on May 16, 2016)
20. Schwochau ME, Hadwiger LA. Stimulation of pisatin production in Pisum sativum by actinomycin D and other compounds. *Archives of Biochemistry and Biophysics.* 1968;126(2):731-733. doi:10.1016/0003-9861(68)90463-3
21. Plants hear sounds, remember, and respond intelligently. Available from http://russgeorge.net/2014/07/01/plants-hear-sounds/ (Accessed on May 16, 2016)
22. Smith B, Randle D, et al. Camalexin-Induced Apoptosis in Prostate Cancer Cells Involves

Alterations of Expression and Activity of Lysosomal Protease Cathepsin D. *Molecules*. 2014;19(4):3988-4005.
23. Stotz HU, Sawada Y, et al, Y. Role of camalexin, indole glucosinolates, and side chain modification of glucosinolate-derived isothiocyanates in defense of Arabidopsis against *Sclerotinia sclerotiorum*. *The Plant Journal*. 2011;67:81–93. doi:10.1111/j.1365-313X.2011.04578.x
24. Revival Soy's start Living Blog. Available from http://blog.soy.com/ (Accessed on May 16, 2016)
25. Glyceollin I – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Glyceollin_I (Accessed on May 16, 2016)
26. Kaplan D, Keen N, Thomason I. Studies on the mode of action of glyceollin in soybean incompatibility to the root knot nematode, *Meloidogyne incognita*. *Physiological Plant Pathology*. 1980;16(3):319-325. doi:10.1016/s0048-4059(80)80003-8
27. Which fruits and vegetables should you eat organic? (Translated from Hebrew). Available from http://hamutziot.com/wp-content/uploads/2014/02/grapes.jpg (Accessed on May 16, 2016)
28. Resveratrol aka the Youth Molecule. Available from https://candimakeupza.wordpress.com/2013/11/21/resveratrol-aka-the-youth-molecule/ (Accessed on May 16, 2016)
29. Hwang D, Lim Y-H. Resveratrol antibacterial activity against *Escherichia coli* is mediated by Z-ring formation inhibition via suppression of FtsZ expression. *Sci. Rep*. 2015;5:10029. doi: 10.1038/srep10029
30. Eat This: Sweet Potatoes | Paleo Leap. Available from http://paleoleap.com/eat-sweet-potatoes/ (Accessed on May 16, 2016)
31. Ipomeamarone – Ganfyd. Available from http://www.ganfyd.org/index.php?title=Ipomeamarone (Accessed on May 16, 2016)
32. Uritani I, Akazawa T. Antibiotic Effect on *Ceratostomella fimbriata* of Ipomeamarone, an Abnormal Metabolite in Black Rot of Sweetpotato. *Science*. 1955;121(3137):216-217. doi:10.1126/science.121.3137.216
33. French Beans Colouring. Available from http://picshype.com/french-beans-images/french-beans-colouring/32251 (Accessed on May 16, 2016)
34. Morrissey JP, Osbourn AE. Fungal Resistance to Plant Antibiotics as a Mechanism of Pathogenesis. *Microbiology and Molecular Biology Reviews*. 1999;63(3):708-724
35. Phaseolin. Available from http://www.spektrum.de/lexikon/biochemie/phaseolin/4716 (Accessed on May 16, 2016)
36. Coda R, Rizzello CG, et al. Long-Term Fungal Inhibitory Activity of Water-Soluble Extracts of *Phaseolus vulgaris* cv. Pinto and Sourdough Lactic Acid Bacteria during Bread Storage. *Applied and Environmental Microbiology*. 2008;74(23):7391-8. doi:10.1128/AEM.01420-08.
37. Vegetable Section. Available from http://www.kisumu-onlineshopping.biz/section_001.html (Accessed on May 16, 2016)
38. (R)-(-)-6-methoxymellein | ChemSpider. Available from http://www.chemspider.com/Chemical-Structure.75266.html (Accessed on May 16, 2016)
39. Kurosaki F, Nishi A. Isolation and antimicrobial activity of the phytoalexin 6-methoxymellein from cultured carrot cells. *Phytochemistry*. 1983;*22*(3):669-672. doi:10.1016/s0031-9422(00)86959-9
40. Wild Wonders of Europe. Available from http://wild-wonders.photoshelter.com/gallery-image/Mountain-flowers-Liechtenstein/G0000Hv7mzVxXjWM/I0000QFEMKD33ddA (Accessed on May 16, 2016)
41. Orchinol | Wikimedia Commons. Available from https://commons.wikimedia.org/wiki/File:Orchinol.png (Accessed on May 16, 2016)
42. Braun R. Orchinol. In *Modern Methods of Plant Analysis / Moderne Methoden der Pflanzenanalyse*, Springer Berlin, Heidelberg. 1963;6:130-4. doi:10.1007/978-3-642-94878-7_7

43. Pit Rot | AHDB Potatoes. Available from http://potatoes.ahdb.org.uk/media-gallery/detail/13213/3360 (Accessed on May 16, 2016)
44. Rishitin | C00003178. Available from http://www.genome.jp/db/pcidb/kna_cpds/3178 (Accessed on May 16, 2016)
45. Sato N, Kitazawa K, Tomiyama K. The role of rishitin in localizing the invading hyphae of *Phytophthora infestans* in infection sites at the cut surfaces of potato tubers. *Physiological Plant Pathology*. 1971;1(3):289-295. doi:10.1016/0048-4059(71)90049-x
46. Cotton 30771. Available from http://www.freegreatpicture.net/still-life-photo/cotton-30771 (Accessed on May 16, 2016)
47. Gossypol – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Gossypol (Accessed on May 16, 2016)
48. Sharma HC, Agarwal RA. Effect of some antibiotic compounds in *Gossypium* on the post-embryonic development of spotted bollworm (*Earias vittella* F.). *Entomologia Experimentalis Et Applicata*. 1982;31(2):225-8. doi:10.1111/j.1570-7458.1982.tb03138.x
49. Roots | Dearborn Market. Available from http://www.dearbornmarket.com/wp-content/uploads/2012/03/parsnip.jpg (Accessed on My 16, 2016)
50. Xanthotoxin analytical standard | SigmaAldrich. Available from http://www.sigmaaldrich.com/catalog/product/sial/56448?lang=en&region=IN (Accessed on May 16, 2016)
51. Alexander N J, McCormick SP, Blackburn JA. Effects of xanthotoxin treatment on trichothecene production in Fusarium sporotrichioides. *Can. J. Microbiol. Canadian Journal of Microbiology*. 2008;54(12):1023-31. doi:10.1139/w08-100
52. Chickpea. Available from http://vugmafood.com/chickpea.html (Accessed on May 16, 2016)
53. Medicarpin | Chemical Book. Available from http://www.chemicalbook.com/ProductChemicalPropertiesCB8182694_EN.htm (Accessed on May 16, 2016)
54. Medicarpin: The Occurrence, Bioactivity in Plant, Biosynthesis and Potential Medicinal Uses. Available from https://commons.wikimedia.org/wiki/User:Nguyenkn (Accessed on May 18, 2016)
55. Cook's Thesaurus: Rice. Available from http://www.foodsubs.com/Rice.html (Accessed May 16, 2016)
56. Ejike C E, Gong M, Udenigwe CC. Phytoalexins from the Poaceae: Biosynthesis, function and prospects in food preservation. *Food Research International*. 2013;52(1):167-177. doi:10.1016/j.foodres.2013.03.012
57. Oryzalexin A. Available from http://www.genome.jp/db/pcidb/kna_cpds/3461 (Accessed on May 16, 2016)
58. Sekido H, Akatsuka T. Mode of Action of Oryzalexin D against *Pyricularia oryzae*. *Agricultural and Biological Chemistry*. 1987;51(7):1967-71. doi:10.1271/bbb1961.51.1967
59. Sorghum seeds. Available from http://dir.indiamart.com/chennai/sorghum-seeds.html (Accessed on May 16, 2016)
60. Nicholson RL, Kollipara SS, Vincent JR, Lyons PC, Cadena-Gomez G. Phytoalexin synthesis by the sorghum mesocotyl in response to infection by pathogenic and nonpathogenic fungi. *Proceedings of the National Academy of Sciences of the United States of America*. 1987;84(16):5520-5524
61. Luteolinidin. Available from https://commons.wikimedia.org/wiki/File:Luteolinidin.svg (Accessed on May 16, 2016)
62. Ibraheem F, Gaffoor I, Chopra S. Flavonoid Phytoalexin-Dependent Resistance to Anthracnose Leaf Blight Requires a Functional *yellow seed1* in *Sorghum bicolor*. *Genetics*. 2010;184(4):915-926. doi:10.1534/genetics.109.111831
63. Organic Maize. Available from https://www.onedegreeorganics.com/ingredients/62?batch=KH2A4N (Accessed on May 16, 2016)
64. Vaughan MM, Christensen S, et al. Accumulation of terpenoid phytoalexins in maize roots is associated with drought tolerance. *Plant Cell Environ*. 2015;38:2195–2207. doi: 10.1111/pce.12482

65. Zealexin A1. Available from http://biocyc.com/compound?orgid=META&id=CPD-13573 (Accessed on May 16, 2016)
66. Arruda RL, Paz ATS, et al. An approach on phytoalexins: function, characterization and biosynthesis in plants of the family Poaceae. *Ciência Rural*. 2016;46(7):1206-16. Epub April 05, 2016. doi: https://dx.doi.org/10.1590/0103-8478cr20151164
67. Reasons to Eat Potato Peels. Available from http://www.green-healer.com/reasons-eat-potato-peels/ (Accessed on May 16, 2016)
68. Bushway RJ, Bureau JL, McGann DF. Alpha-Chaconine and Alpha-Solanine Content of Potato Peels and Potato Peel Products. *Journal of Food Science*. 1983;48:84–6. doi: 10.1111/j.1365-2621.1983.tb14794.x
69. Alpha-Solanine. Available from http://www.mpbio.com/images/product-images/molecular-structure/158222.png (Accessed on May 16, 2016)
70. Amanpour R, Abbasi-Maleki S. Antibacterial effects of *Solanum tuberosum* peel ethanol extract in vitro. *Journal of HerbMed Pharmacology*. 2015;4(2):45-48.
71. Why Not To Eat Papaya During Pregnancy? Available from https://indswift.wordpress.com/2015/03/07/why-not-to-eat-papaya-during-pregnancy/ (Accessed on May 17, 2016)
72. Danielone. Available from http://pic0.molbase.net/molpic/02/21/02214807.png?162x157 (Accessed on May 17, 2016)
73. Echeverri F, Torres F, et al. Danielone, a phytoalexin from papaya fruit. *Phytochemistry*. 1997;44(2):255-256. doi:10.1016/s0031-9422(96)00418-9
74. Taste It. Available from http://www.tasteit.pt/sites/default/files/styles/large/public/favas_0.jpg?itok=NVraa9Ni (Accessed on May 17, 2016)
75. Wyerone Acid | ChemSpider. Available from http://www.chemspider.com/Chemical-Structure.30776870.html (Accessed on May 17, 2016)
76. Mansfield JW, Deverall BJ. Changes in wyerone acid concentrations in leaves of *Vicia faba* after infection by *Botrytis cinerea* or *B.fabae*. *Annals of Applied Biology*. 1974;77:227–235. doi: 10.1111/j.1744-7348.1974.tb01399.x
77. Plantain Flatbread. Available from http://www.powercakes.net/3-ingredient-plantain-flatbread/ (Accessed on May 17, 2016)
78. Luis JG, Echeverri F, et al. Irenolone and emenolone: Two new types of phytoalexin from Musa paradisiaca. *The Journal of Organic Chemistry J. Org. Chem.* 1993;58(16):4306-8. doi:10.1021/jo00068a027
79. Irenolone. Available from http://www.arkpharminc.com/arkpharm/files/images/goodsPic/products_images/AK169475.gif (Accessed on May 17, 2016)
80. Cécile AE, Philippe L, et al. Involvement of phenolic compounds in the susceptibility of bananas to crown rot. A review. *Base* [En ligne]. 2012;16(3):393-404.
81. Abayasekara CL, Adikaram NKB, et al. *Phyllosticta musarum* Infection-Induced Defences Suppress Anthracnose Disease Caused by *Colletotrichum musae* in Banana Fruits cv "Embul." *The Plant Pathology Journal*. 2013;29(1):77-86. doi:10.5423/PPJ.OA.06.2012.0081
82. Harvested Oat Roots. Available from https://oatnotes.files.wordpress.com/2014/12/2015-02-10-12-30-46.jpg (Accessed on May 17, 2016)
83. Avenacin A-1. Available from http://pic3.molbase.net/molpic/02/48/2489788.png?488x294 (Accessed on May 17, 2016)
84. Carter JP, Spink J, et al. Isolation, Characterization, and Avenacin Sensitivity of a Diverse Collection of Cereal-Root-Colonizing Fungi. *Applied and Environmental Microbiology*. 1999;65(8):3364-3372.
85. The Top 5 Tomato Producing Countires. Available from https://top5ofanything.com/uploads/2015/05/Tomatoes.jpg (Accessed on May 17, 2015)
86. Neilson EH, Goodger JQ, et al. Plant chemical defense: At what cost? *Trends in Plant Science*. 2013;18(5):250-8. doi:10.1016/j.tplants.2013.01.001
87. Mitchell G, Gattuso M, et al. Tomatidine Inhibits Replication of *Staphylococcus aureus*

Small-Colony Variants in Cystic Fibrosis Airway Epithelial Cells. *Antimicrobial Agents and Chemotherapy*. 2011;55(5):1937-1945. doi:10.1128/AAC.01468-10.
88. Organic Dried Fruit. Available from http://www.rawguru.com/store/images/C/Black%20Zante-Currants-Raw-Organic%20-%2016%20oz-t.jpg (Accessed on May 17, 2016)
89. Sakuranetin – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Sakuranetin (Accessed on May 17, 2016)
90. Hibiscus. Available from http://thumbs4.ebaystatic.com/d/l225/m/mvAIWxhFAX7Jdu7qGg8Mlzw.jpg (Accessed on May 17, 2016)
91. Protocatechuic Acid – Wikipedia, The Free Encyclopedia. Available from https://en.wikipedia.org/wiki/Protocatechuic_acid#Biological_effects (Accessed on May 18, 2016)
92. Protocatechuic acid | Chemspider. Available from http://www.chemspider.com/Chemical-Structure.71.html (Accessed on May 17, 2016)
93. Tseng T, Kao T, et al. Induction of apoptosis by Hibiscus protocatechuic acid in human leukemia cells via reduction of retinoblastoma (RB) phosphorylation and Bcl-2 expression. *Biochemical Pharmacology.* 2000;60(3):307-315. doi:10.1016/s0006-2952(00)00322-1
94. Garlic. Avaliable from http://www.petinsurance.com/healthzone/pet-articles/pet-health-toxins/~/media/All%20PHZ%20Images/Article%20images/GarlicBulbCloves.ashx (Accessed on May 18, 2016)
95. Allicin. Available from https://upload.wikimedia.org/wikipedia/commons/a/af/R-allicin-2D-skeletal.png (Accessed on May 18, 2016)
96. Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic. *Microbes and Infection.* 1999;1(2):125-9. doi:10.1016/s1286-4579(99)80003-3
97. Labarnum. Available from http://www.rogerstreesandshrubs.com/MediaPath/116C49BCA1E54827BEEADB156AFA0603.jpg (Accessed on May 18, 2016)
98. Sato H, Tahara S, et al. Isoflavones from pods of *Laburnum anagyroides*. *Phytochemistry.* 1995;39(3):673-6. doi:10.1016/0031-9422(95)00029-7
99. Luteone. Available from https://upload.wikimedia.org/wikipedia/commons/thumb/e/e2/Luteone.svg/200px-Luteone.svg.png (Accessed on May, 18, 2016)
100. Akter K, Barnes EC, et al. Antimicrobial and antioxidant activity and chemical characterisation of *Erythrina stricta* Roxb. (Fabaceae). *Journal of Ethnopharmacology*. 2016;185:171-181. doi:10.1016/j.jep.2016.03.011
101. Tulips. Available from http://ekladata.com/HzLxftPCaiIDu0kSH8IJbmPLGD0.png (Accessed on May 18, 2016)
102. Tuliposide A. Available from http://chem.sis.nlm.nih.gov/chemidplus/structure/19870-30-5 (Accessed on May 18, 2016)
103. Shigetomi K, Omoto S, et al. Asymmetric Total Synthesis of 6-Tuliposide B and Its Biological Activities against Tulip Pathogenic Fungi. *Bioscience, Biotechnology and Biochemistry*. 2011;75(4):718-722. doi:10.1271/bbb.100845
104. Dried peels of Grapefruit. Available from http://www.starwest-botanicals.com/media/catalog/product/2/0/201553-31_18.jpg (Accessed on May 18, 2016)
105. Castro-Vazquez L, Alañón ME, et al. Bioactive Flavonoids, Antioxidant Behaviour, and Cytoprotective Effects of Dried Grapefruit Peels (*Citrus paradisi* Macf.). *Oxidative Medicine and Cellular Longevity*. 2016;8915729:12. doi:10.1155/2016/8915729
106. Wang D-M, Yang Y-J, et al. Naringin Enhances CaMKII Activity and Improves Long-Term Memory in a Mouse Model of Alzheimer's Disease. *International Journal of Molecular Sciences*. 2013;14(3):5576-86. doi:10.3390/ijms14035576
107. Alam MA, Subhan N, et al. Effect of Citrus Flavonoids, Naringin and Naringenin, on Metabolic Syndrome and Their Mechanisms of Action. *Advances in Nutrition*. 2014;5(4):404-417. doi:10.3945/an.113.005603
108. Purkayastha RP. Phytoalexin Production and Plant Defense. *Proc. Indian natn. Sci.*

Acad. 1996;B62(1):51-64

109. Yoshikawa, M. Diverse modes of action of biotic and abiotic phytoalexin elicitors. *Nature*. 1978;275(5680):546-7. doi:10.1038/275546a0

110. Minami E. Oligosaccharide Elicitors as Plant Protectants | GlycoWord. Available from http://www.glycoforum.gr.jp/science/word/glycobiology/PS-02E.html (Accessed on May 17, 2016)

111. Eckardt NA. Induction of Phytoalexin Biosynthesis: WRKY33 Is a Target of MAPK Signaling. *The Plant Cell*. 2011;23(4):1190. doi:10.1105/tpc.111.230413

112. González-Lamothe R, Mitchell G, et al. Plant Antimicrobial Agents and Their Effects on Plant and Human Pathogens. *International Journal of Molecular Sciences*. 2009;10(8):3400-19. doi:10.3390/ijms10083400

113. Myint KB, Sing LC, et al. Tannic Acid as Phytochemical Potentiator for Antibiotic Resistance Adaptation. *APCBEE Procedia.* 2013;7:175-181. doi:10.1016/j.apcbee.2013.08.030

114. Bernal P, Molina-Santiago C, et al. Antibiotic adjuvants: identification and clinical use. *Microbial Biotechnology*. 2013;6(5):445-449. doi:10.1111/1751-7915.12044

115. Kerstin A. Wolff, Marissa Sherman and Liem Nguyen (2011). Potentiation of Available Antibiotics by Targeting Resistance – An Emerging Trend in Tuberculosis Drug Development, Drug Development - A Case Study Based Insight into Modern Strategies, Dr. Chris Rundfeldt (Ed.), InTech, DOI: 10.5772/27702. Available from: http://www.intechopen.com/books/drug-development-a-case-study-based-insight-into-modern-strategies/potentiation-of-available-antibiotics-by-targeting-resistance-an-emerging-trend-in-tuberculosis-drug