Chapter 5
Plant Natural Products as a Potential Source of Antimicrobial Agents: An Overview and a Glimpse on Recent Developments

Mohd. Shahid, Fazal K. Dar, Abdulrahman Y. Ismaeel, Ali Al-Mahmeed, Khalid Al Sindi, Abida Malik, and Haris M. Khan

5.1 Introduction

Looking back to the literature, anyone would realize that human beings were utilizing the potential of natural products of plant origin to cure infections, for instance, ancient cultures in India, Greece, Serbia etc. were using moulds and other plants as a remedy to treat infections (Anonymous 2012a).

In 1877, Pasteur and Joubert recognized the potential of "microbial" products as therapeutic agents that could inhibit the growth of *Anthrax* bacilli. However, the milestone in the field of antimicrobial agents is believed to be the advent of

M. Shahid, M.B.B.S., M.D., Ph.D., FNZIMLS (✉)
Department of Medical Microbiology, Immunology and Infectious Diseases, College of Medicine and Medical Sciences, Arabian Gulf University, PO Box 26671, Manama, Kingdom of Bahrain

Department of Pathology, Blood Bank and Laboratory Medicine, King Hamad University Hospital, Busaiteen, Kingdom of Bahrain

Department of Microbiology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
e-mail: shahidsahar@yahoo.co.in; mohammeds@agu.edu.bh; mohammad.shahid@khuh.org.bh

F.K. Dar • A.Y. Ismaeel • A. Al-Mahmeed
Department of Medical Microbiology, Immunology and Infectious Diseases, College of Medicine and Medical Sciences, Arabian Gulf University, PO Box 26671, Manama, Kingdom of Bahrain

K. Al Sindi
Department of Pathology, Blood Bank and Laboratory Medicine, King Hamad University Hospital, Busaiteen, Kingdom of Bahrain

A. Malik • H.M. Khan
Department of Microbiology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

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penicillin by Alexander Fleming from the fungus *Penicillium* (Shahid et al. 2009a, b). Subsequently the potential for antibacterial and antifungal properties was searched in other fungi and higher plants.

However due to selection pressure, as a result of increasing and irrational usage of existing antimicrobial agents, the microorganisms have started expressing resistance to these compounds. Therefore, scientists are continuously trying to search for newer compounds, harboring antimicrobial properties, derived from the plant species. In this chapter, the potential of plant species to yield newer antibacterial agents will be illustrated with an emphasis on compounds exclusively isolated in very recent years.

5.2 Antibacterial Potential in Plant Natural Products

We previously published an exhaustive literature review on antibacterial potential of plant natural products, and the readers are encouraged to read the same for a descriptive list of plant species harboring antibacterial potential and the chemical compounds, reported by various workers (Shahid et al. 2009a). In this section some of the plant species recently reported (2011–2012) to bear the antibacterial potential will briefly be reviewed.

5.2.1 Quercus dilatata *L.*

Quercus dilatata L., known as "Holly Oak", is commonly found in Afghanistan, Pakistan, and temperate Himalayas from Kashmir to Nepal (Anonymous 2012b).

The tree is up to 20 m in height. The leaves are elliptic-ovate to broadly lanceolate (4–12×1.6–5.5 cm), entire to spiny toothed, and containing nerves 9–12 pairs, forked at the extremities (Anonymous 2012b). Few other species of *Quercus* were reported to possess antibacterial activity (Jamil et al. 2012) and used to treat infected wounds and burns (Jamil et al. 2012). However, in a recent study by Jamil et al. (2012), the crude methanolic extract of aerial parts of *Quercus dilatata* L. was described, as a first report, to possess antibacterial activity against all of the bacterial species tested, namely, *Escherichia coli*, *Bacillus subtilis*, *Salmonella setuball*, *Bordetella bronchiseptica*, *Staphylococcus aureus* and *Micrococcus luteus* (Jamil et al. 2012). Further bioassay guided fractionation and phytochemical analysis of the extracts demonstrated that ethyl acetate, acetone, ethanol and 50 % methanol fractions contained the activity; the most active fraction was reported as ethanol extract by the authors (Jamil et al. 2012). Phytochemical analysis demonstrated the presence of alkaloids as a major component responsible for the activity and HPLC analysis of the active partitioned fraction (Ethanol) demonstrated a distinct peak not corresponding to the

peaks of other natural compounds reported from *Quercus* viz. ascorbic acid, quercitrin, gallic acid and rutin; this suggests the presence of a different compound that needs to be elucidated structurally (Jamil et al. 2012).

This recent study by Jamil et al. reports the presence of a new antibacterial compound in *Quercus dilatata* L. that needs to be characterized further for its exact identification.

5.2.2 Gnetum montanum

Gnetum montanum is a vine commonly found in China and also in Nepal, Thailand, Vietnam and India. It belongs to Family *Gnetaceae* and commonly known as Gam Nui or Sot Nui (Anonymous 2012c). It is an evergreen dioecious climber that is branching and swollen at nodes (Anonymous 2012d). Leaves are dark green, oblong-ovate and 12–30 cm in length, while the plant produces a red colored fruit of 1.5 × 1 cm diameter. Very recently Martin and colleagues described antibacterial potential of *Gnetum montatum* extract against *Pseudomonas aeruginosa* wild-type strain PAO1 (Martin et al. 2011). The authors described the presence of various new natural products such as 6a,7-didehydro-1,9,10-trihydroxy-2-methoxy-6-methylaporphinium trifluoroacetate, *N*-methyllaudanosolinium trifluoroacetate, 3′-hydroxy-*N*, *N*-dimethylcoclaurinium trifluoroacetate, and 1,9,10-trihydroxy-2-methoxy-6-methylaporphinium trifluoroacetate along with the previously known natural products such as latifolian A and magnocurarine. The anti-Pseudomonal activity was reported in the natural product latifolian A (Martin et al. 2011).

Recent years have really witnessed a much faster appearance of antibiotics resistance in bacteria as opposed to the development of antibacterial compounds. The drug-industry has tried its best to respond to the challenge of rising resistance and recently developed some novel β-lactams compounds such as ceftobiprole, ceftaroline, etc. However, the pace of antimicrobial drug development has drastically slowed during the last decade with only few newer agents available. The scientists are now looking forward towards plant natural products as an alternative to combat this threatening issue of antibiotics resistance. To that end, various research groups have recently tried to explore the antimicrobial potential of plant extracts. Table 5.1 summarizes some of the examples of the recently explored plant species for their antibacterial potential.

5.3 Antimycobacterial Potential

It is a well known fact that >40 % of the world population is infected with tubercle bacilli, however a diminutive percentage of the infective population develops tuberculosis (TB). According to a recent review, approximately eight million new

Table 5.1 Some of the very recently described plant species with antibacterial activity

Plant species	Active extract	Compound responsible	Organism	References
Abrus schimperi	Ethanol	Pendulone	*Staphylococcus aureus*; MRSA	Rahman et al. (2011)
Crotalaria retusa	Ethanol		*Pseudomonas aeruginosa*	Devendra et al. (2012)
Elephantopus scaber L.	Ethanol (root)		*S. aureus*, *E. coli*, *P. aeruginosa*	Anitha et al. (2012)
	Ethanol (leaves)		*E. faecalis*, *P. mirabilis*, *S. typhi*, *Enterobacter* spp.	
	Chloroform		*Bacillus cereus*	
Hemigraphis colorata	Benzene		*Acinetobacter* spp., *S. aureus*	Anitha et al. (2012)
Chelidonium majus L.	Ethanol	8-hydroxydihydrosanguinarine 8-hydroxydihydrochelerythrine	ESBL-producing bacteria	Guo et al. (2008)
Sida alba L.	Polyhenol-fraction		*Enterococcus faecalis*	Konate et al. (2012)
Artocarpus heterophyllus	Latex		*Pseudomonas aeruginosa*	Siritapetawee et al. (2012)

cases and two million deaths occur each year and *Mycobacterium tuberculosis* alone accounts for more mortality than any other single bacterial species (Bueno et al. 2011). The World Health Organization (WHO) embarked to reduce the global burden of TB and bring down the TB deaths and prevalence to half of the existing situation by 2015 through its Stop TB Strategy and supporting the Global Plan to Stop TB (Anonymous 2012e). Although the treatment options are available, the emergence of the Mutli-drug-resistance (MDR) and extensively drug-resistance (XDR) in *Mycobacterium tuberculosis* has worried the clinicians in recent years. Keeping in mind the emergence of drug-resistance in tubercle bacilli, especially the emergence of XDR, where we have very little options for the treatment, it is worth finding out the natural plant products as an alternate for the cure. Several plant species have been reported to possess anti-Mycobacterial activities, to name a few, *Indigofera longeracemosa* (Bueno et al. 2011), *Calophyllum lanigerum* (Bueno et al. 2011), *Engelhardia roxburghiana* (Lin et al. 2005) and *Lantana hispida* (Jimenez-Arellanes et al. 2007). Detailed reviews on the current aspect describing the plants and the compounds responsible for the antimycobacterial activity are discussed in some of the recent review articles (Bueno et al. 2011; Guzman et al. 2012). This area seems promising to search for the novel anti-Mycobacterial plant products, especially active against MDR and XDR tuberculosis.

5.4 Antifungal Potential in Plant Natural Products

Since the introduction of one of the oldest antifungal classes of antibiotics, polyene macrolides (nystatin and amphotericin B), and subsequently the other classes such as imidazoles (clotrimazole, miconazole, ketoconazole), first generation triazoles (fluconazole, itraconazole) and second generation triazoles (voriconazole, posaconazole, ravuconazole), the fungi have evolved tremendously with the development of resistance to these antifungal agents. The industry attempted to respond, on one hand, by developing liposomal formulations (liposomized amphotericin B and nystatin) in order to develop methods for targeted drug delivery to minimize the adverse effects and development of resistance, and on the other hand by developing newer classes of antifungal drugs such as echinocandins, caspofungin, micafungin, anidulafungin, pneumocandins, pradimicins and benanomicins, nikkomycins and sordarins. However, the fungi are continuously evolving and there is a need to search for newer compound to combat the emerging problem of antifungal resistance (Shahid and Tripathi 2011). To that end, scientists are continuously searching the herbal plants for their potential antifungal action. Table 5.2 summarizes the recently reported plant species to possess antifungal potential that could be used as potential candidates for the future development of antifungal compounds.

Table 5.2 Some of the very recently described plant species with antifungal activity

Plant species	Active extract	Compound responsible	Organism	References
Polygonum ferrugineum Wedd.	DCM extract	Cardamonin	*Epidermophyton floccosum*	Lopez et al. (2011)
Momordica charantia	Ethanol	–	*Candida* spp.	Santos et al. (2012)
Origanum vulgare	Essential oil	–	Contaminant molds	Chaves-Lopez et al. (2012)
Equisetum arvense	Crude extract	–	*Aspergillus flavus*	Garcia et al. (2012)
Stevia rebaudiana	Crude extract	–	*Fusarium verticilliodes*	Garcia et al. (2012)
Zizyphus jujube	Methanol, n-hexane Chloroform, ethyl acetate	–	*Penicillium notatum*	Ahmad et al. (2011)
	n-hexane	–	*Aspergillus niger*, *Fusarium oxysporum*, *Rhizopus stolonifer*	
Cassia fistula L.	Crude (seed extract)	–	*Candia albicans*	Jothy et al. (2011)

5.5 Antiparasitic Potential in Plant Natural Products

5.5.1 Abrus schimperi

The Genus *Abrus* is a flowering plant of the family Fabaceae containing around 18 species. Abrus schimperi is a flora of tropical Africa. In a recent study by Rahman et al. (2011), the authors described the anti-Leishmanial activity of the ethanolic extract of Abrus schimperi against promastigotes of *Leishmania donovani*. The authors reported the presence of two isoflavanquinones, amorphaquinone and pendulone with IC50 values of 0.63 and 0.43 μg/ml, respectively. The authors also reported the antiplasmodial activity in the two extract against *Plasmodium falciparum* D6 and W2 strains (Rahman et al. 2011).

5.5.2 Momordica charantia

Momordica charantia is commonly known as bitter melon or bitter gourd. It is a tropical and subtropical vine of the family *Cucurbitaceae* and is commonly grown in Asia, Africa, and the Caribbean for its edible fruits. In a recent study, Santos and colleagues (2012) described anti-Trypanosomal activity in the ethanolic extract from leaves of *Momordica charantia* against epimastigotes of *Trypanosoma cruzi*; the IC50 was reported as 46.06 μg/ml (Santos et al. 2012). The authors suggested its anti-Trypanosomal activity (against epimastigotes) with moderate toxicity in comparison to the available drugs (Nifurtimox and Beznidazole).

During our search of recent literature, we noticed numerous other interesting studies reporting plant species to possess anti-parasitic activities. For instance, Nibret and Wink (2011) screened 30 Ethiopian-plant species, those were used in traditional medicine, for anti-Trypanosomal activity. They found five plants namely, *Dovyalis abyssinica*, *Albizia schimperiana*, *Ocimum urticifolium*, *Acokanthera schimperi* and *Chenopodium ambrosioides* to possess activity against Trypanosoma brucei brucei. In another study, Nibret et al. (2010) screened 20 Tanzanian-plant species for anti-Tryponosomal activity and found *Entadrophragma bussei*, *Securidaca longepedunculata*, *Warburgia salutaris*, *Zanha Africana* and *Zanthoxylum chalybeum* to possess the activity. In a recent study, Okokon et al. (2012) described anti-Plasmodial activity in the leaf-extracts from *Clausena anisata*.

5.6 Utility of Plant-Secondary Metabolites (PSMs) in Reversing Multi-drug Resistance (MDR)

Bacteria evolved producing multi-drug resistance to several antibiotics as a result of selection pressure. There are several mechanisms by which bacteria can produce resistance to these antimicrobial agents (Cowan 1999; Shahid et al. 2009c).

These escaping strategies in a resistant bacterium could be by many ways, some of them are mentioned below:

(A) modification of normal drug-binding proteins such as penicillin binding proteins (PBPs) or bypassing of the normal PBPs
(B) impermeability of outer membranes of the bacteria to drugs
(C) production of enzymes that inactivates drugs, such as β-lactamases
(D) ability to pump out drugs by efflux pumps

Recent years have witnessed the role of plant-secondary metabolites (PSMs) as the inhibitors of ABC transporter system and hence play a role in reversing antimicrobial resistance. Secondary metabolites, such as terpenoids, function as substrate for P-gp (in cancer cells) and its orthologue (in parasites), and for other ABC transporter systems such as AtrB (in fungi) and NorA efflux pump (in *Staphylococcus aureus*) and thus serve as inhibitors of ABC transporters (Andrade et al. 2000; Smith et al. 2007; Wink et al. 2012). During our search of literature, we noticed an important and exhaustive recent review on the current theme published by Wink et al. (2012) describing various PSMs that were reported to reverse the resistance in cancer cells and microbes to cytotoxic and antimicrobial agents, respectively. We encourage interested readers to go through that "must read" article to get better insight into the subject. Since our present compilation deals with the antimicrobial potential in plant-natural products, we intend to summarize here, from the existing literature, the potential role of PSMs in reversing antimicrobial resistance in some of the medically important microorganisms such as Staphylococcus aureus (including methicillin-resistant *S. aureus*), *Mycobacterium tuberculosis* (including multidrug resistant (MDR) strains) and other medically important microorganisms. Table 5.3 summarizes the PSMs, their source of isolation and their activity on ABC transporters of target microorganisms.

5.7 Antiviral Potential in Plant Natural Products with Special Reference to HIV and Influenza Virus

Despite the passage of almost three decades since the discovery of Human Immunodeficiency Virus (HIV) and AIDS, the field of Medicine is still struggling to find any effective cure for this disease syndrome. Many researchers sought plant natural products for anti-HIV activity.

Several classes of the plant natural products, including terpenoids, flavanoids and alkaloids have been reported to possess anti-HIV activity (in vitro) that possibly targeted reverse transcriptase/integrase/protease/viral fusion etc. We encourage interested readers to read the articles by Tan et al. (1991), Pengsuparp et al. (1995), and Cowan (1999) for detailed description of various plant species reported to possess ant-HIV activities and also for their reported targets of action.

During our search of recent literature, we noticed numerous new reports describing various other plant species having anti-HIV potential and those can be utilized

Table 5.3 Some of the plant secondary metabolites (PSMs) reported to possess antimicrobial activities

Microorganism	PSM	Source	Activity	References
Staphylococci				
S. aureus	Calodenin B, dihydrocalodenin B, other dimeric proanthocyanidins	*Ochna macrocalyx*	Inhibit MDR	Tang et al. (2003); Wink et al. (2012)
	Chrysosplenol-D, chrysosplenetin	*Artemisia annua* L.	Synergistic inhibition of MDR	Stermitz et al. (2002); Wink et al. (2012)
	Tiliroside	Platanus orientalis, Herissantia tiubae	Inhibits NorA efflux protein	Falcao-Silva et al. (2009); Wink et al. (2012)
MRSA[a]	Emodin	*Rheum palmatum*	Synergistic activity with oxacillin in MRSA	Lee et al. (2010); Wink et al. (2012)
	Canthin-6-one, 8-hydroxy-canthin-6-one	*Allium neapolitanum*	Inhibit MDR	O'Donnell and Gibbons (2007); Wink et al. (2012)
	Chelerythrine	*Zanthoxylum clava-herculis*	Reversal of drug resistance	Gibbons et al. (2003); Wink et al. (2012)
	5-Methoxyhydnocarpine, pheophorbide A	*Hydnocarpus kurzii*, *Berberis* spp.	Inhibitor of NorA MDR pump	Stermitz et al. (2000; 2001); Wink et al. (2012)
	N-trans-feruloyl 4′-O-methyldopamine	*Mirabilis jalapa*	Inhibits *S. aureus* over expressing NorA pump	Michalet et al. (2007)
	Totarol	*Podocarpus totara*	Inhibits NorA efflux pump	Smith et al. (2007)
Mycobacterium tuberculosis	Aegicerin	*Clavija procera*	Reversal of MDR in resistant- *M. tuberculosis*	Rojas et al. (2006)
	Piperine	*Piper nigrum*	Inhibits over expression of Mycobacterial efflux protein (Rv1258c)	Sharma et al. (2010)
	Vasicine acetate, 2-acetyl benzylamine	*Adhatoda vasica*	Inhibits MDR starins	Ignacimuthu and Shanmugam (2010)
Acinetobacter baumannii	Ellagic acid, tannic acid	Several plant species	Inhibition of efflux pump	Chusri et al. (2009); Wink et al. (2012)
Candida albicans	Plagiochin	*Marchantia polymorpha*	Reversal of the efflux pump	Guo et al. (2008); Wink et al.(2012)

[a]*MRSA* Methicillin-resistant *S. aureus*

Table 5.4 Plant species reported to possess anti-HIV activity in the recent literature

Plant species	References
Aegle marmelos	Sabde et al. (2011)
Asparagus racemosus	Sabde et al. (2011)
Coleus forskohlii	Sabde et al. (2011)
Rubia cordifolia	Sabde et al. (2011)
Ocimum sanctum Linn.	Rege et al.(2010)
Tinospora cordifolia (Willd) Miers. Ex Hook.f. &Thoms	Rege et al. (2010)
Avicennia officinalis Linn.	Rege et al. (2010)
Rhizophora mucronata Lam.	Rege et al. (2010)
Azadirachta indica	Awah et al. (2011)
Bubine alooides (L.) Willd.	Klos et al. (2009)
Leonotisleonurus (L.) R.Br.	Klos et al. (2009)

in future to prepare novel anti-HIV compounds. Readers are also encouraged to read a recent review article by Filho et al. (2010) where the authors described a list of 275 species of medicinal plants that were studied for the activity on HIV-1-protease.

A recent study was done by Sabde et al. (2011) directed towards assessment of anti-HIV activity of various extracts prepared from Indian medicinal plants as immunomodulators. Ninety-two extracts were prepared from 23 plants. Anti-HIV activity was measured in a human CD4+ T-cell line, CEM-GFP cells infected with HIV-1NL4.3. Nine extracts of eight different plants significantly reduced viral production in CEM-GFP cells infected with HIV-1NL4.3. *Aegle marmelos*, *Argemone mexicana*, *Asparagus racemosus*, *Coleus forskohlii*, *and Rubia cordifolia* demonstrated promising anti-HIV potential and were investigated for their active principles.

A recent review by Singh et al. (2011) described numerous plant species possessing anti-HIV activity, their active ingredients, assay model used and the mechanism(s) of action. Table 5.4 describes few more recently reported plant species to harbor anti-HIV potential.

Recent years have witnessed a tremendous health-threat through recent H1N1 influenza pandemic. Although officially declared in August 2010 as the end of pandemic by World Health Organization (WHO), the threat has not disappeared for its revisit (Shahid 2012). Keeping in mind the global burden of such a disease, researchers are continuously searching the natural products for their action against influenza virus. During the search for recent literature, we found some published studies that reported for the anti-influenza activities in plant extracts. Some of those studies will briefly be mentioned in this section. Shin and colleagues (2010) tested various Korean medicinal plants for their potential activities against influenza viruses and reported a promising plant species, *Agrimonia pilosa*, for its activity against all three subtypes of human influenza virus, including H1N1 and H3N2 influenza A subtypes and influenza B virus. Moreover, authors reported strong inhibitory effect (in ovo) of the extract on H9N2 avian influenza virus when tested in embryonated eggs. The plant species reported by Shin et al. (2010) could be a promising candidate for drug development against the influenza viruses. Haidari et al. (2009)

reported the anti-viral activity in pomegranate polyphenol extract (PPE) against H3N2 influenza virus. Similarly, the catechins in the green tea have been reported to possess anti-viral activity against influenza virus (Song et al. 2005).

In a recent study by Sood et al. (2012), the authors described anti-viral activity in the crude extracts of leaves and bark of Eugenia jambolana Lam. against the highly pathogenic avian influenza (H5N1) virus.

In nutshell, probably the nature has provided us the cure for most of the diseases in our environment, and it is our duty to search for cure of those ailments. To that end, natural products from the medicinal plant species should extensively be searched for as to combat these life-threatening illnesses.

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References

Ahmad, B., Khan, I., Bashir, S., Azam, S., & Ali, N. (2011). The antifungal, cytotoxic, antitermite and insecticidal activities of Zizyphus jujube. *Pakistan Journal of Pharmaceutical Sciences, 24*(4), 489–493.

Andrade, A. C., Del Sorbo, G., Van Nistelrooy, J. G., & Waard, M. A. (2000). The ABC transporter AtrB from Aspergillus nidulans mediates resistance to all major classes of fungicides and some natural toxic compounds. [Research Support, Non-U.S. Gov't]. *Microbiology, 146*(Pt 8), 1987–1997.

Anitha, V. T., Antonisamy, J. M., & Jeeva, S. (2012). Anti-bacterial studies on Hemigraphis colorata (Blume) H.G. Hallier and Elephantopus scaber L. *Asian Pacific Journal of Tropical Medicine, 5*(1), 52–57. doi:10.1016/S1995-7645(11)60245-9.

Anonymous. (2012a, 14 June). *History of penicillin*. Retrieved June 17, 2012, from http://en.wikipedia.org/wiki/History_of_penicillin

Anonymous. (2012b). *Flora of Pakistan*. Retrieved June 14, 2012, from http://www.efloras.org/florataxon.aspx?flora_id=5&taxon_id=242424827

Anonymous. (2012c). Retrieved June, 14, 2012, from http://florawww.eeb.uconn.edu/200202424.html

Anonymous. (2012d). *Pictorial identification manual of cites plants in India*. Retrieved June, 14, 2012, from http://www.bsienvis.nic.in/citesplant.htm#Gnetummontanum

Anonymous. (2012e). *Pharmacovigilance for anti-TB medicines*. Retrieved June 14, 2012, from http://www.who.int/tb/en/

Awah, F. M., Uzoegwu, P. N., & Ifeonu, P. (2011). In vitro anti-HIV and immunomodulatory potentials of *Azadirachta indica* (Meliaceae) leaf extract. *African Journal of Pharmacy and Pharmacology, 5*(11), 1353–1359.

Bueno, J., Coy, E. D., & Stashenko, E. (2011). Antimycobacterial natural products–an opportunity for the Colombian biodiversity [Research Support, Non-U.S. Gov't; Review]. *Revista Española de Quimioterapia, 24*(4), 175–183.

Chaves-Lopez, C., Martin-Sanchez, A. M., Fuentes-Zaragoza, E., Viuda-Martos, M., Fernandez-Lopez, J., Sendra, E., Sayas, E., & Angel Perez Alvarez, J. (2012). Role of Oregano (Origanum vulgare) essential oil as a surface fungus inhibitor on fermented sausages: Evaluation of its effect on microbial and physicochemical characteristics. *Journal of Food Protection, 75*(1), 104–111. doi:10.4315/0362-028X.JFP-11-184.

Chusri, S., Villanueva, I., Voravuthikunchai, S. P., & Davies, J. (2009). Enhancing antibiotic activity: A strategy to control Acinetobacter infections [Research Support, Non-U.S. Gov't]. *Journal of Antimicrobial Chemotherapy, 64*(6), 1203–1211. doi:10.1093/jac/dkp381.

Cowan, M. M. (1999). Plant products as antimicrobial agents [Review]. *Clinical Microbiology Reviews, 12*(4), 564–582.

Devendra, B. N., Srinivas, N., & Solmon, K. S. (2012). A comparative pharmacological and phytochemical analysis of in vivo & in vitro propagated Crotalaria species [Comparative Study]. *Asian Pacific Journal of Tropical Medicine, 5*(1), 37–41. doi:10.1016/S1995-7645(11)60242-3.

Falcao-Silva, V. S., Silva, D. A., Souza Mde, F., & Siqueira-Junior, J. P. (2009). Modulation of drug resistance in Staphylococcus aureus by a kaempferol glycoside from Herissantia tiubae (Malvaceae) [Research Support, Non-U.S. Gov't]. *Phytotherapy Research, 23*(10), 1367–1370. doi:10.1002/ptr.2695.

Filho, J. R., de Sousa Falcao, H., Batista, L. M., Filho, J. M., & Piuvezam, M. R. (2010). Effects of plant extracts on HIV-1 protease [Review]. *Current HIV Research, 8*(7), 531–544.

Garcia, D., Ramos, A. J., Sanchis, V., & Marin, S. (2012). Effect of Equisetum arvense and Stevia rebaudiana extracts on growth and mycotoxin production by Aspergillus flavus and Fusarium verticillioides in maize seeds as affected by water activity [Research Support, Non-U.S. Gov't]. *International Journal of Food Microbiology, 153*(1–2), 21–27. doi:10.1016/j.ijfoodmicro.2011.10.010.

Gibbons, S., Leimkugel, J., Oluwatuyi, M., & Heinrich, M. (2003). Activity of Zanthoxylum clava-herculis extracts against multi-drug resistant methicillin-resistant Staphylococcus aureus (mdr-MRSA). *Phytotherapy Research, 17*(3), 274–275. doi:10.1002/ptr.1112.

Guo, X. L., Leng, P., Yang, Y., Yu, L. G., & Lou, H. X. (2008). Plagiochin E, a botanic-derived phenolic compound, reverses fungal resistance to fluconazole relating to the efflux pump [Research Support, Non-U.S. Gov't]. *Journal of Applied Microbiology, 104*(3), 831–838. doi:10.1111/j.1365-2672.2007.03617.x.

Guzman, J. D., Gupta, A., Bucar, F., Gibbons, S., & Bhakta, S. (2012). Antimycobacterials from natural sources: Ancient times, antibiotic era and novel scaffolds [Research Support, Non-U.S. Gov't; Review]. *Frontiers in Bioscience, 17*, 1861–1881.

Haidari, M., Ali, M., Ward Casscells, S., 3rd, & Madjid, M. (2009). Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. *Phytomedicine, 16*(12), 1127–1136. doi:10.1016/j.phymed.2009.06.002.

Ignacimuthu, S., & Shanmugam, N. (2010). Antimycobacterial activity of two natural alkaloids, vasicine acetate and 2-acetyl benzylamine, isolated from Indian shrub Adhatoda vasica Ness. leaves [Research Support, Non-U.S. Gov't]. *Journal of Biosciences, 35*(4), 565–570.

Jamil, M. D., Haq, I. U. D., Mirza, B. D., & Qayyum, M. D. (2012). Isolation of antibacterial compounds from Quercus dilatata L. through bioassay guided fractionation. *Annals of Clinical Microbiology and Antimicrobials, 11*(1), 11. doi:10.1186/1476-0711-11-11.

Jimenez-Arellanes, A., Meckes, M., Torres, J., & Luna-Herrera, J. (2007). Antimycobacterial triterpenoids from Lantana hispida (Verbenaceae) [Research Support, Non-U.S. Gov't]. *Journal of Ethnopharmacology, 111*(2), 202–205. doi:10.1016/j.jep.2006.11.033.

Jothy, S. L., Zakaria, Z., Chen, Y., Lau, Y. L., Latha, L. Y., Shin, L. N., & Sasidharan, S. (2011). Bioassay-directed isolation of active compounds with antiyeast activity from a Cassia fistula seed extract [Research Support, Non-U.S. Gov't]. *Molecules, 16*(9), 7583–7592. doi:10.3390/molecules16097583.

Klos, M., van de Venter, M., Milne, P. J., Traore, H. N., Meyer, D., & Oosthuizen, V. (2009). In vitro anti-HIV activity of five selected South African medicinal plant extracts [Research Support, Non-U.S. Gov't]. *Journal of Ethnopharmacology, 124*(2), 182–188. doi:10.1016/j.jep.2009.04.043.

Konate, K., Mavoungou, J. F., Lepengue, A. N., Aworet-Samseny, R. R., Hilou, A., Souza, A., Dicko, M. H., & M'batchi, B. (2012). Antibacterial activity against beta- lactamase producing Methicillin and Ampicillin-resistants Staphylococcus aureus: Fractional Inhibitory Concentration Index (FICI) determination. *Annals of Clinical Microbiology and Antimicrobials, 11*(1), 18. doi:10.1186/1476-0711-11-18.

Lee, Y. S., Kang, O. H., Choi, J. G., Oh, Y. C., Keum, J. H., Kim, S. B., Jeong, G. S., Kim, Y. C., Shin, D. W., & Kwon, D. Y. (2010). Synergistic effect of emodin in combination with ampicillin or oxacillin against methicillin-resistant Staphylococcus aureus [Research Support, Non-U.S.Gov't].*PharmaceuticalBiology,48*(11),1285–1290.doi:10.3109/13880201003770150.

Lin, W. Y., Peng, C. F., Tsai, I. L., Chen, J. J., Cheng, M. J., & Chen, I. S. (2005). Antitubercular constituents from the roots of Engelhardia roxburghiana [Research Support, Non-U.S. Gov't]. *Planta Medica, 71*(2), 171–175. doi:10.1055/s-2005-837786.

Lopez, S. N., Furlan, R. L., & Zacchino, S. A. (2011). Detection of antifungal compounds in Polygonum ferrugineum Wedd. extracts by bioassay-guided fractionation. Some evidences of their mode of action [Research Support, Non-U.S. Gov't]. *Journal of Ethnopharmacology, 138*(2), 633–636. doi:10.1016/j.jep.2011.09.038.

Martin, F., Grkovic, T., Sykes, M. L., Shelper, T., Avery, V. M., Camp, D., Quinn, R. J., & Davis, R. A. (2011). Alkaloids from the Chinese vine Gnetum montanum [Research Support, Non-U.S. Gov't]. *Journal of Natural Products, 74*(11), 2425–2430. doi:10.1021/np200700f.

Michalet, S., Cartier, G., David, B., Mariotte, A. M., Dijoux-franca, M. G., Kaatz, G. W., Stavri, M., & Gibbons, S. (2007). N-caffeoylphenalkylamide derivatives as bacterial efflux pump inhibitors [Research Support, Non-U.S. Gov't]. *Bioorganic & Medicinal Chemistry Letters, 17*(6), 1755–1758. doi:10.1016/j.bmcl.2006.12.059.

Nibret, E., & Wink, M. (2011). Trypanocidal and cytotoxic effects of 30 Ethiopian medicinal plants. *Zeitschrift für Naturforschung. Section C, 66*(11–12), 541–546.

Nibret, E., Ashour, M. L., Rubanza, C. D., & Wink, M. (2010). Screening of some Tanzanian medicinal plants for their trypanocidal and cytotoxic activities [Research Support, Non-U.S. Gov't]. *Phytotherapy Research, 24*(6), 945–947. doi:10.1002/ptr.3066.

O'Donnell, G., & Gibbons, S. (2007). Antibacterial activity of two canthin-6-one alkaloids from Allium neapolitanum [Research Support, Non-U.S. Gov't]. *Phytotherapy Research, 21*(7), 653–657. doi:10.1002/ptr.2136.

Okokon, J. E., Etebong, E. O., Udobang, J. A., & Essien, G. E. (2012). Antiplasmodial and analgesic activities of Clausena anisata. *Asian Pacific Journal of Tropical Medicine, 5*(3), 214–219. doi:10.1016/S1995-7645(12)60027-3.

Pengsuparp, T., Cai, L., Constant, H., Fong, H. H., Lin, L. Z., Kinghorn, A. D., Pezzuto, J. M., Cordell, G. A., Ingolfsdottir, K., Wagner, H., et al. (1995). Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase [Research Support, U.S. Gov't, P.H.S.]. *Journal of Natural Products, 58*(7), 1024–1031.

Rahman, A. A., Samoylenko, V., Jain, S. K., Tekwani, B. L., Khan, S. I., Jacob, M. R., Midiwo, J. O., Hester, J. P., Walker, L. A., & Muhammad, I. (2011). Antiparasitic and antimicrobial isoflavanquinones from Abrus schimperi [Research Support, N.I.H., Extramural; Research Support, U.S. Gov't, Non-P.H.S.]. *Natural Product Communications, 6*(11), 1645–1650.

Rege, A. A., Ambaye, R. Y., & Deshmukh, R. A. (2010). *In-vitro* testing of anti-HIV activity of some medicinal plants. *Indian Journal of Natural Products and Resources, 1*(2), 193–199.

Rojas, R., Caviedes, L., Aponte, J. C., Vaisberg, A. J., Lewis, W. H., Lamas, G., Sarasara, C., Gilman, R. H., & Hammond, G. B. (2006). Aegicerin, the first oleanane triterpene with wide-ranging antimycobacterial activity, isolated from Clavija procera [Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.]. *Journal of Natural Products, 69*(5), 845–846. doi:10.1021/np0505541.

Sabde, S., Bodiwala, H. S., Karmase, A., Deshpande, P. J., Kaur, A., Ahmed, N., Chauthe, S. K., Brahmbhatt, K. G., Phadke, R. U., Mitra, D., Bhutani, K. K., & Singh, I. P. (2011). Anti-HIV activity of Indian medicinal plants [Letter; Research Support, Non-U.S. Gov't]. *Journal of Natural Medicines, 65*(3–4), 662–669. doi:10.1007/s11418-011-0513-2.

Santos, K. K., Matias, E. F., Sobral-Souza, C. E., Tintino, S. R., Morais-Braga, M. F., Guedes, G. M., Santos, F. A., Sousa, A. C., Rolon, M., Vega, C., de Arias, A. R., Costa, J. G., Menezes, I. R., & Coutinho, H. D. (2012). Trypanocide, cytotoxic, and antifungal activities of Momordica charantia. *Pharmaceutical Biology, 50*(2), 162–166. doi:10.3109/13880209.2011.581672.

Shahid, M. (2012). On the roads to H1N1 pandemic era: Drive safe and fearless using colour-coded masks. *Asian Pacific Journal of Tropical Medicine, 5*(4), 333–334. doi:10.1016/S1995-7645(12)60052-2.

Shahid, M., & Tripathi, T. (2011). *Recent developments in anti-fungal agents: Perspective for combination therapies in treatment of invasive fungal infections*. Saarbrücken: Lambert Academic Publications (LAP).

Shahid, M., Shahzad, A., Sobia, F., Sahai, A., Tripathi, T., Singh, A., Khan, H. M., & Umesh. (2009a). Plant Natural Products as a potential source for antibacterial agents: Recent trends. *Anti-Infective Agents in Medicinal Chemistry, 8*, 211–225.

Shahid, M., Shahzad, A., Tripathi, T., Sobia, F., Sahai, A., Singh, A., Malik, A., Shujatullah, F., & Khan, H. M. (2009b). Recent trends in plant-derived antifungal agents. *Anti-Infective Agents in Medicinal Chemistry, 8*(1), 36–49.

Shahid, M., Sobia, F., Singh, A., Malik, A., Khan, H. M., Jonas, D., & Hawkey, P. M. (2009c). Beta-lactams and beta-lactamase-inhibitors in current- or potential-clinical practice: A comprehensive update [Research Support, Non-U.S. Gov't; Review]. *Critical Reviews in Microbiology, 35*(2), 81–108. doi:10.1080/10408410902733979.

Sharma, S., Kumar, M., Nargotra, A., Koul, S., & Khan, I. A. (2010). Piperine as an inhibitor of Rv1258c, a putative multidrug efflux pump of Mycobacterium tuberculosis [Research Support, Non-U.S. Gov't]. *Journal of Antimicrobial Chemotherapy, 65*(8), 1694–1701. doi:10.1093/jac/dkq186.

Shin, W. J., Lee, K. H., Park, M. H., & Seong, B. L. (2010). Broad-spectrum antiviral effect of Agrimonia pilosa extract on influenza viruses [Research Support, Non-U.S. Gov't]. *Microbiology and Immunology, 54*(1), 11–19. doi:10.1111/j.1348-0421.2009.00173.x.

Singh, J. S., Abhilash, P. C., Singh, H. B., Singh, R. P., & Singh, D. P. (2011). Genetically engineered bacteria: An emerging tool for environmental remediation and future research perspectives [Research Support, Non-U.S. Gov't; Review]. *Gene, 480*(1–2), 1–9. doi:10.1016/j.gene.2011.03.001.

Siritapetawee, J., Thammasirirak, S., & Samosornsuk, W. (2012). Antimicrobial activity of a 48-kDa protease (AMP48) from Artocarpus heterophyllus latex [Research Support, Non-U.S. Gov't]. *European Review for Medical and Pharmacological Sciences, 16*(1), 132–137.

Smith, E. C., Kaatz, G. W., Seo, S. M., Wareham, N., Williamson, E. M., & Gibbons, S. (2007). The phenolic diterpene totarol inhibits multidrug efflux pump activity in Staphylococcus aureus [Research Support, Non-U.S. Gov't]. *Antimicrobial Agents and Chemotherapy, 51*(12), 4480–4483. doi:10.1128/AAC.00216-07.

Song, J. M., Lee, K. H., & Seong, B. L. (2005). Antiviral effect of catechins in green tea on influenza virus [Research Support, Non-U.S. Gov't]. *Antiviral Research, 68*(2), 66–74. doi:10.1016/j.antiviral.2005.06.010.

Sood, R., Swarup, D., Bhatia, S., Kulkarni, D. D., Dey, S., Saini, M., & Dubey, S. C. (2012). Antiviral activity of crude extracts of Eugenia jambolana Lam. against highly pathogenic avian influenza (H5N1) virus. *Indian Journal of Experimental Biology, 50*(3), 179–186.

Stermitz, F. R., Lorenz, P., Tawara, J. N., Zenewicz, L. A., & Lewis, K. (2000). Synergy in a medicinal plant: Antimicrobial action of berberine potentiated by 5′-methoxyhydnocarpin, a multidrug pump inhibitor [Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.]. *Proceedings of the National Academy of Sciences of the United States of America, 97*(4), 1433–1437. doi:10.1073/pnas.030540597.

Stermitz, F. R., Beeson, T. D., Mueller, P. J., Hsiang, J., & Lewis, K. (2001). Staphylococcus aureus MDR efflux pump inhibitors from a Berberis and a Mahonia (sensu strictu) species. *Biochemical Systematics and Ecology, 29*(8), 793–798.

Stermitz, F. R., Scriven, L. N., Tegos, G., & Lewis, K. (2002). Two flavonols from Artemisa annua which potentiate the activity of berberine and norfloxacin against a resistant strain of Staphylococcus aureus [Letter; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.]. *Planta Medica, 68*(12), 1140–1141. doi:10.1055/s-2002-36347.

Tan, G. T., Pezzuto, J. M., Kinghorn, A. D., & Hughes, S. H. (1991). Evaluation of natural products as inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase [Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.]. *Journal of Natural Products, 54*(1), 143–154.

Tang, S., Bremner, P., Kortenkamp, A., Schlage, C., Gray, A. I., Gibbons, S., & Heinrich, M. (2003). Biflavonoids with cytotoxic and antibacterial activity from Ochna macrocalyx [Research Support, Non-U.S. Gov't]. *Planta Medica, 69*(3), 247–253. doi:10.1055/s-2003-38478.

Wink, M., Ashour, M. L., & El-Readi, M. Z. (2012). Secondary metabolites from plants inhibiting ABC transporters and reversing resistance of cancer cells and microbes to cytotoxic and antimicrobial agents. *Frontiers in Microbiology, 3*, 130. doi:10.3389/fmicb.2012.00130.