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Review

Phytochemicals as chemotherapeutic agents and antioxidants: Possible solution to the control of antibiotic resistant verocytotoxin producing bacteria

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The interest in plants with antimicrobial properties has been revived due to current problems associated with the use of antibiotics with the increased prevalence of multidrug resistant (MDR) bacterial strains. Some emerging species of bacteria such as *Escherichia coli* 0517: H7 and *Acinetobacter* species that are verocytotoxin producers present further chemotherapeutic challenges because of the increased level of toxin production in medium when challenged with antibiotics. The abundant medicinal plant resources and their antioxidant properties and possibly undiscovered novel modes of action can be a solution to the control of multidrug resistant verocytotoxic bacteria.

Key words: Antimicrobial, multi-drug resistance, chemotherapy.

INTRODUCTION

Phytochemicals are defined as bioactive non-nutrient plant compounds in fruits, vegetables, grains, and other plant foods that have been linked to reducing the risk of major chronic diseases. The word 'phyto-' is derived from the Greek *phyto* which means - plant (Liu, 2004). The presence of these bioactive components are said to confer them with resistance against bacterial, fungal and pesticidal pathogens. These bioactive components are said to be responsible for the antimicrobial effects of plant extracts *in vitro* (Abo et al., 1991; Nweze et al., 2004).

The interest in plants with antimicrobial properties has been revived due to current problems associated with the use of antibiotics with the increased prevalence of multidrug resistant (MDR) strains of a number of pathogenic bacteria such as methicillin resistant *Staphylococcus aureus, Helicobacter pylori,* and MDR *Klebsiela pneumonia* (Voravuthikunchai and Kitpipit, 2003). On the other hand, infection with *Escherichia coli* 0157: H7 involves the risk stimulation of verocytotoxin (VT) production (Yoh et al., 1997, 1999). Herbal remedies are viewed as reemerging health aid in a number of countries (UNESCO, 1997). This can be traced to both the increasing cost of prescription drugs, for the maintenance of personal health and antibiotic-resistant strains in the case of infectious diseases (Levy, 1998; Van den Bogaard et al., 2000; Smolinski et al., 2003). In industrialized countries, the extraction and development of many drugs, and chemotherpeutics from medicinal plants have been increasing (UNESCO, 1998). Complications in the use of antibiotics in the treatment of hemolytic uremic syndrome (HUS), and thrombocytopenic purpura (TTP) encouraged researchers to find effective medicinal plants as effective treatment for *E. coli* 0157: H7 and related infections (Sandvig, 2001; Voravuthikunchai et al., 2005; Abong'o and Momba, 2009).

Long before mankind discovered the existence of microbes, the idea that certain plants had healing potential, and that they contained what we would currently charac-

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terize as antimicrobial principles, was well accepted. Since antiquity, man has used plants to treat common infectious diseases and some of these traditional medicines are still included as part of the habitual treatment of various maladies. Since the levels of sanitation and hygiene are low for the majority of people in Africa compared to people in the First World countries, African people are therefore, to a large extent, exposed to a wider array of microbial pathogens, which increases their susceptibility to bacterial infections. However, because the African land is rich with medicinal herbs, they often resort to treating such infections with the local and indigenous plants, in situations where commercial drugs are not available or are too expensive (Fennel et al., 2004; McGaw et al., 2005; Yagoub, 2008; Lewu and Afolayan, 2009). For example, the use of bearberry (*Arctostaphylos uva-ursi*) and cranberry juice (*Vaccinium macrocarpon*) to treat urinary tract infections is reported in different manuals of phytotherapy, while species such as lemon balm (*Melissa officinalis*), garlic (*Allium sativum*) and tee tree (*Melaleuca alternifolia*) are described as broad-spectrum antimicrobial agents (Heinrich et al., 2004). Different plant parts and components (roots, leaves, stem barks, flowers or their combinations, essential oils) have been employed in the treatment of infectious pathologies in the respiratory system, urinary tract, gastrointestinal and biliary systems, as well as on the skin (Rojas et al., 2001; R´ıos and Recio, 2005; Adekunle and Adekunle, 2009). Various chemical compounds (phytochemicals) with antibacterial activities exist in plants. Phytochemicals have been isolated and characterized from fruits such as grapes and apples, vegetables such as broccoli and onion, spices such as turmeric, beverages such as green tea and red wine, as well as many other sources. These compounds are used by the plants as natural defences against bacteria, fungi and pests (Doughari and Obidah, 2008). In general, phenolics have been shown to be the predominant active chemical in plants, with gram positive bacteria being the most susceptible germs.

Common methods used in the evaluation of the antibacterial and antifungal activities of plant extracts and essential oils, include the agar diffusion method (paper disc and well), the dilution method (agar and liquid broth) and the turbidimetric and impedimetric monitoring of microbial growth (R´ıos and Recio, 2005). These methods are simple to carry out under laboratory conditions, thus removing any barrier to the possible investigation of more plants for novel antibiotics.

MECHANISM OF ACTION OF PHYTOCHEMICALS

Different mechanisms of action of phytochemicals have been suggested. They either act as antioxidants, or may modulate gene expression and signal transduction pathways (Kris-Etherton et al., 2002; Manson, 2003; Surh, 2003). They may either be used as chemotherapeutic or chemopreventive agents with chemoprevention referring to the use of agents to inhibit, reverse, or retard tumorogenesis. In this sense, chemopreventive phytochemicals are applicable to cancer therapy, since molecular mechanisms may be common to both chemoprevention and cancer therapy (D'Incalci et al., 2005; Sarkar and Li, 2006).

Molecular mechanisms of herb–drug interaction have been investigated. The most notable involves the ATP-binding cassette drug transporters such as P-glycoprotein (You and Moris, 2007) and the drug metabolizing enzymes (known as phase I and phase II enzymes), especially cytochrome P450 3A4 (CYP3A4) (Pal and Mitra, 2006; Meijerman et al., 2006). Multiple molecular targets of dietary phytochemicals have been identified, from pro- and anti-apoptotic proteins, cell cycle proteins, cell adhesion molecules, protein kinases, transcription factors to metastasis and cell growth pathways (Awad and Bradford, 2005; Aggarwal and Shishodia, 2006; Choi and Friso, 2006). Polyphenols particularly are among the diverse phytochemicals that have the potential to inhibit carcinogenesis (Liu, 2004). The polyphenolic phytochemicals are virtually ubiquitous in plant materials and may occur at very high levels. Phenolics in plants are mostly synthesized from phenylalanine via the action of phenylalanine ammonia lyase (PAL). They are very important to plants and have multiple functions. The most important role of plant phenolics may be in plant defense against pathogens and herbivore predators, and thus are applied in the control of human pathogenic infections (Puupponen-Pimiä et al., 2008). With the discovery of health benefits of plant polyphenols, it has been proposed to optimize the phenolic content of the diet so as to obtain favorable consequences for general health of the population (Parr and Bolwell, 2000).

Phytochemicals including plant polyphenols that show health benefits may act via similar or different mechanisms in humans as those functional in plants. This mechanism may be novel to those of synthetic antibiotics for the control antibiotic resistant pathogenic strains. Phytochemicals may also modulate transcription factors (Andreadi et al., 2006), redox-sensitive transcription factors (Surh et al., 2005), redox signaling, and inflammation (Rahman et al., 2006). As an example, nitric oxide (NO), a signaling molecule of importance in inflammation, is modulated by plant polyphenols and other botanical extracts (Chan and Fong, 1999; Shanmugam et al., 2008). Many phytochemicals have been classified as phytoestrogens, with health-promoting effects resulting in the phytochemicals to be marketed as nutraceuticals (Moutsatsou, 2007).

Phytochemicals such as epigallocatechin-3-gallate (EGCG) from green tea, curcumin from turmeric, and resveratrol from red wine tend to aim at a multitude of molecular targets. It is because of these characteristics

that definitive mechanisms of action are not available despite decades of research (Francis et al., 2002). The multi-target nature of phytochemicals may be beneficial in overcoming cancer drug resistance. This multi-faceted mode of action probably hinders the cancer cell's ability to develop resistance to the phytochemicals. It has also been demonstrated that EGCG has inhibitory effects on the extracellular release of VT from *E. coli* 0157: H7 (Voravuthikunchai and Kitpipit, 2003). Ethanol pericarp extracts from *Punica granatum* was also reported to inhibit VT production in periplasmic space and cell supernatant. Mechanisms responsible for this are yet to be understood, however the active compounds from the plant are thought to interfere with the transcriptional and translational processes of the bacterial cell (Voravuthikunchai and Kitpipit, 2003). More work is needed to be done in order to establish this assumption.

SAFETY CONCERNS FOR PHYTOCHEMICALS

Plants are natural reservoir of medicinal agents almost free from the side effects normally caused by synthetic chemicals (Fennel et al., 2004). The World Health Organization estimates that herbal medicine is still the main stay of about 75-80% of the world population, mainly in the developing countries for primary health care because of better cultural acceptability, better compatibility with the human body, and lesser side-effects (Kamboj, 2000; Yadav and Dixit, 2008). The over-use of synthetic drugs with impurities resulting in higher incidence of adverse drug reactions, has motivated mankind to go back to nature for safer remedies. Due to varied locations where these plants grow, coupled with the problem of different vanacular names, the World Health Organization published standards for herbal safety to minimize adulteration and abuse (WHO, 1999).

A number of modern drugs have been isolated from natural sources and many of these isolations were based on the uses of the agents in traditional medicine (Rizvi et al., 2009). Antimicrobial properties of crude extracts prepared from plants have been described and such reports had attracted the attention of scientists worldwide (Falodun et al., 2006; El- Mahmood and Amey, 2007; El-Mahmood, 2009). Herbs have been used for food and medicinal purposes for centuries and this knowledge have been passed on from generation to generation (Adedapo et al., 2005). This is particularly evident in the rural areas where infectious diseases are endemic and modern health care facilities are few and far; thus, compelling the people to nurse their ailments using local herbs. Herbal treatments have been adjudged to be relatively safe (WHO, 1999). For instance, daily oral doses of epigallocatechin-3-gallate (EGCG) for 4 weeks at 800 mg/day in 40 volunteers only caused minor adverse effects (Phillipson, 2007). In a 90-day study of polyphenon E (a formulation of green tea extract with 53% EGCG), the oral no-effect level (NOEL) values are 90 mg/kg/day for rats and 600 mg/kg/day for dogs (Boocock et al., 2007). For curcumin, given to cancer patients at 3600 mg/day for 4 months or 800 mg/day for 3 months, only minor adverse effects are seen. For resveratrol, a single oral dose at 5 g in 10 volunteers only causes minor adverse effects (Boocock et al., 2007). Though herbs are relatively safe to use, their combined use with orthodox drugs should be done with extreme caution. Concomitant use of conventional and herbal medicines is reported to lead to clinically relevant herb–drug interactions (Liu et al., 2009). The two may interact either pharmacokinetically or pharmacodynamically resulting into adverse herbal-drug interactions (Izzo, 2005). St John's wort (*Hypericum perforatum*), used for the treatment of mild to moderate depression, interacts with digoxin, HIV inhibitors, theophylline and warfarin. Some medicinal herbs, when ingested, either affect cytochrome P450 isoenzymes by which drugs are metabolized, or, phosphoglycoprotein transporter systems that affect drug distribution and excretion. Concurrent use of some herbal medicines with other medicines may either lower blood plasma concentrations of medicinal drugs, possibly resulting in suboptimal therapeutic amounts, or lead to toxic concentrations in the blood, sometimes with fatal consequences (Phillipson, 2007).

Despite this observation however, it has been reported that phytochemicals act in synergy with chemotherapeutic drugs in overcoming cancer cell drug resistance and that the application of specific phytochemicals may allow the use of lower concentrations of drugs in cancer treatment with an increased efficacy (Liu, 2004).

Another advantage with phytochemicals is that, among an estimated 10,000 secondary products (natural pesticides), it has been proposed that human ancestors evolved a generalized defense mechanism against low levels of phytochemicals to enable their consumption of many different plant species containing variable levels of natural pesticides (carcinogens) without subsequent ill health (Liu, 2004). Traces of phytochemicals found in fruits and vegetables may potentiate the immune system and help to protect against cancer (Trewavas and Stewart, 2003). Phytochemicals show biphasic dose responses on mammalian cells. Though at high concentrations they can be toxic; sub-toxic doses may induce adaptive stress response (Ames and Gold, 1991). This includes the activation of signaling pathways that result in increased expression of genes encoding cytoprotective proteins. It is therefore suggested that hermetic mechanisms of action may underlie many of the health benefits of phytochemicals including their action against cancer drug resistance (Mattson, 2008).

Several phytoconstituents also act as antioxidants. Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species otherwise called, free radicals such as singlet oxygen, super-

oxide anion, peroxyl radicals, hydroxyl radicals and peroxynitrite which results in oxidative stress leading to cellular damage (Mattson and Cheng, 2006). Natural antioxidants play a key role in health maintenance and prevention of the chronic and degenerative diseases, such as atherosclerosis, cardiac and cerebral ischema, carcinogenesis, neurodegenerative disorders, diabetic pregnancy, rheumatic disorder, DNA damage and ageing (Uddin et al., 2008; Jayasri et al., 2009). The antioxidants act by reacting with free oxygen radicals. The free radicals are metastable chemical species, which tend to trap electrons from the molecules in the immediate surroundings. These radicals, if not scavenged effectively in time, may damage crucial biomolecules like lipids, proteins (including those present in all membranes), and DNAs resulting in abnormalities leading to disease conditions (Uddin et al., 2008). Thus, free radicals are implicated in a number of diseases including tumor inflammation (tumorigenesis), hemorrhagic shock, atherosclerosis, diabetes, infertility, gastrointestinal ulcerogenesis, asthma, rheumatoid arthritis, cardiovascular disorders, cytic fibrosis, neurodegenerative diseases (eg. parkinsonism, Alzheimer's diseases), AIDS and even early senescence (Chen et al., 2006; Uddin et al., 2008). Although in relatively insufficient amounts, the human body produces antioxidant metabolites (such as glutathione, melatonin, etc) and antioxidant enzymes (such as superoxide dismutase, catalases, etc) which are essential for preventing oxidative stress resulting from free radical accumulation in body tissues. Therefore, this insufficiency had to be compensated for by making use of natural exogenous antioxidants, such as vitamin C, vitamin E, flavones, β-carotene and natural products in plants (Sen, 1995; Madsen and Bertelsen, 1995; Rice-Evans et al., 1997; Diplock et al., 1998).

Plants contain a wide variety of free radicals scavenging molecules including phenols, flavonoids, vitamins, terpenoids that are rich in antioxidant activity (Madsen and Bertelsen, 1995; Cai and Sun, 2003). Many plants, citrus fruits and leafy vegetables are the source of ascorbic acid, vitamin E, caratenoids, flavanols and phenolics which possess the ability to scavenge the free radicals in human body. Significant antioxidant properties have been recorded in phytochemicals that are necessary for the reduction in the occurrence of many diseases (Hertog and Feskens, 1993; Anderson and Teuber, 2001). Many dietary polyphenolic constituents derived from plants are more effective antioxidants *in vitro* than vitamins E or C, and thus might contribute significantly to protective effects *in vivo* (Rice-Evans and Miller, 1997; Jayasri et al., 2009). Studies to uncover other novel plant products especially those with potential activity against verocytotoxic bacteria has become very necessary. This is due to the emergence of bacteria producing these toxins and the abundance of predisposing factors ranging from fecal contamination of food and water sources to low level of hygiene and sanitation consciousness in the developing countries. The ready availability of these plants should be a motivating factor in embarking of such a research.

METHODS OF STUDYING PHYTOCHEMICALS

A successful strategy for investigating plants for biologically active compounds proved to be initial screening followed by bioassay-guided fractionation to aid isolation of active constituents (Perumal et al., 1999; Mattson and Cheng, 2006). Apart from the traditional methods of screening for biological activity using disc diffusion and agar dilution methods, the separation, identification and structure determination of biologically active compounds has been facilitated by continual development of chromatographic and spectroscopic methods of analysis (Bohlin and Bruhn, 1999). These analytical techniques are becoming more and more sophisticated (Hostettmann and Lea, 1987; Philipson, 2007). The nuclear magnetic resonance (NMR) techniques are employed for establishing connectivities between neighbouring protons and establishinh C-H bonds. Insensitive nuclei enhanced by polarization transfer (INEPT) technique is also being used for long range heteronuclear correlations over multiple bondings. The application of thin layer chromatography (TLC), high performance chromatography (HPLC) and HPLC coupled with ultraviolet (UV) photodiode array detection, liquid chromatography-ultraviolet (LC-UV), liquid chromatography mass spectrophotometry (LCMS), electrospray (ES) and liquid chromatography-nuclear magnetic resonance (LC-NMR) techniques for the separation and structure determination of antifungal and antibacterial plant compounds is on the increase frequently (Oleszek and Marston, 2000; Bohlin and Bruhn, 1999). Currently available are chromatographic and spectroscopic techniques in new drug discovery from natural products. Of recent, computer modelling has also been introduced in spectrum interpretation and the generation of chemical structures meeting the spectral properties of bioactive compounds obtained from plants (Vlietinck, 2000). The computer systems utilize 1H, 13C, 2D-NMR, IR and MS spectral properties (Philipson, 2007). Libraries of spectra can be searched for comparison with complete or partial chemical structures. Hyphenated chromatographic and spectroscopic techniques are powerful analytical tools that are combined with high throughput biological screening in order to avoid re-isolation of known compounds as well as for structure determination of novel compounds. Hyphenated chromatographic and spectroscopic techniques include LC–UV–MS, LC–UV–NMR, LC–UV–ES–MS and GC–MS (Oleszek and Marston, 2000; Philipson, 2007). More work is however needed in developing simple methods of identification, purification and formulation of bioactive plant components

Table 1. Drugs based on natural products at different stages of development.

Development stage	Plant	Bacterial	Fungal	Animal	Semi-synthetic	Total
Preclinical	46	12	7	7	27	99
Phase I	14	5	0	3	8	30
Phase II	41	4	0	10	11	66
Phase III	5	4	0	4	13	26
Pre-registration	2	0	0	0	2	4
Total	108	25	7	24	61	225

Source: Harvey, 2008.

into drugs for the control of verocytotoxin producing antimicrobial resistant bacteria and other pathogenic bacteria.

Future prospects of phytochemicals as sources of antimicrobial chemotherapeutic agents

There are few disadvantages associated with natural products research. These include difficulties in access and supply, complexities of natural product chemistry and inherent slowness of working with natural products. In addition, there are concerns about intellectual property rights, and the hopes associated with the use of collections of compounds prepared by combinatorial chemistry methods. Despite these limitations, over a 100 natural-product-derived compounds are currently undergoing clinical trials and at least 100 similar projects are in preclinical development (Phillipson, 2007). Among these products the highest number are from plant origin (Table 1). Most are derived from plants and microbial sources. The projects based on natural products are predominantly being studied for use in cancer or as anti-infectives. There is also a growing interest in the possibility of developing products that contain mixtures of natural compounds from traditionally used medicines (Charlish, 2008), while a defined mixture of components extracted from green tea (Veregen TM) has been approved by the US Food and Drug Administration (FDA) and has recently come on the market.

Most of the leads from natural products that are currently in development have come from either plant or microbial sources. Earlier publications have pointed out that relatively little of the world's plant biodiversity has been extensively screened for bioactivity and that very little of the estimated microbial biodiversity has been available for screening (Harvey, 2000, 2008). Hence, more extensive collections of plants (and microbes) could provide many novel chemicals for use in drug discovery assays. With the growing realization that the chemical diversity of natural products is a better match to that of successful drugs than the diversity of collections of synthetic compounds and with the global emergence of multidrug resistant pathogens (Feher and Schmidt, 2003), the interest in applying natural chemical diversity to drug discovery appears to be increasing once again (Galm and Shen, 2007).

With advances in fractionation techniques to isolate and purify natural products (for example, counter-current chromatography) (Harvey, 2008) and in analytical techniques to determine structures (Singh and Barrett, 2006), screening of natural product mixtures is now more compatible with the expected timescale of high-throughput screening campaigns. Singh and Barrett (2006) pointed out that pure bioactive compounds can be isolated from fermentation broths in less than 2 weeks and that the structures of more than 90% of new compounds can be elucidated within 2 weeks. With advances in NMR techniques, complex structures can be solved with much less than 1 mg of compound. It has recently been demonstrated that it is possible to prepare a screening library of highly diverse compounds from plants with the compounds being pre-selected from an analysis of the Dictionary of Natural Products to be drug-like in their physicochemical properties (Oleszek and Marston, 2000; Harvey, 2008). It will be interesting to see if such a collection proves to be enriched in bioactive molecules. Several alternative approaches are also being explored in efforts to increase the speed and efficiency with which natural products can be applied to drug discovery. For instance, there is an attraction to screen the mixtures of compounds obtained from extracts of plant material or from microbial broths to select extracts from primary screens that are likely to contain novel compounds with the desired biological activity using the concept of 'differential smart screens'. This approach involves screening extracts of unknown activity against pairs of related receptor sites. By the comparison of the ratios of the binding potencies at the two receptor sites for a known selective ligand and for an extract, it is possible to predict which extract was likely to contain components with the appropriate pharmacological activity (McGaw et al., 2005; Harvey, 2008; Okigbo et al., 2009). Another approach is the use of 'chemical-genetics profiling' (Harvey, 2008). In this method, by building up a database of the effects of a wide range of known compounds, it is possible to interrogate drugs with unknown mechanisms or mixtures of compounds such as natural

product mixtures. The technique highlighted unexpected similarities in molecular effects of unrelated drugs (for example, amiodarone and tamoxifen) and also revealed potential anti-fungal activity of crude extracts. This activity was confirmed by isolation and testing of defined compounds, stichloroside and theopalauamide (Figure 1).

Because these compounds are not structurally similar, they would not have been expected to act via the same biological target, thus providing more chances for a very versatile drug component with high efficacy against antibiotic resistant bacteria. It has been reported that despite the popularity of chemical drugs, herbal medicine in Africa and the rest of the world has continued to be practiced due to richness of certain plants in varieties of secondary metabolites such as alkaloids, flavonoids, tannins and terpenoids (Cowan, 1999; Lewis and Ausubel, 2006; Adekunle and Adekunle, 2009). Stapleton et al. (2004) reported that aqueous extracts of green tea (*Camellia sinensis*) reversed methicillin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) and also, to some extent, reduced penicillin resistance in beta-lactamase-producing *Staphylococcus aureus*. Also, Betoni et al. (2006) reported synergistic interactions between extracts of guaco (*Mikania glomerata*), guava (*Psidium guajava*), clove (*Syzyguim aromaticum*), garlic (*Allium sativum*), lemon grass (*Cymbopogon citratus*), ginger (*Zingiber officinale*), cargueja (*Baccharis trimera*), mint (*Mentha pieria*), and some antibiotics against *S. aureus*. However, these are preliminary investigations and more works are needed to actually determine the active ingredients in these plants extracts and this may help in improving management of the different infectious diseases that are developing resistance to commonly used antibiotics and possibly to verocytotoxuic bacteria. Furthermore, toxicological studies can also be carried out to determine the reliance on these herbs without many side effects.

Researchers have also devised cluster of chemically related scaffolds which are very useful in guiding the synthesis of new compounds. In an attempt to combine the advantages of virtual screening of chemically diverse natural products and their synthetic analogues (scaffolds) with the rapid availability of physical samples for testing, an academic collaboration has established the Drug Discovery Portal (http://www.ddp.strath.ac.uk/). This brings together a wide variety of compounds from academic laboratories in many different institutions in a database that can be used for virtual screening. Academic biology groups can also propose structures as targets for virtual screening with the Portal's database (and with conventional commercially available databases). Access to the Portal is free for academic groups and the continued expansion of the chemical database means that there is a valuable and growing coverage of chemical space through many novel chemical compounds (Feher and Schmidt, 2003; Galm and Shen, 2007; Harvey, 2008).

Despite all of the advances made by the pharmaceutical industry in the development of novel and highly effective medicines for the treatment of a wide range of diseases, there has been a marked increase in the use of herbal medicines even including the more affluent countries of the world. Germany has the largest share of the market in Europe and it was reported that the sales of herbal medicinal products (HMPs) in 1997 were US$ 1.8 billion (Barnes et al., 2007). Numerous scientific medical/pharmaceutical books have been published in recent years aiming to provide the general public and healthcare professionals with evidence of the benefits and risks of herbal medicines (Barnes et al., 2007; Phillipson, 2007). The pharmaceutical industry has met the increased demand for herbal medicines by manufacturing a range of herbal medicinal products (HMPs) many of which contain standardized amounts of specific natural products. In the 1950s, it would not have been possible to predict that in 50 years time there would be a thriving industry producing HMPs based on the public demand for herbal medicines. To date, European pharmacopoeia has even published up to 125 monographs on specific medicinal herbs with another 84 currently in preparation (Mijajlovic et al., 2006; Phillipson, 2007. The monographs are meant to provide up-to-date knowledge of phytochemistry for defining the chemical profiles of medicinal herbs and an understanding of analytical tests for identification of the herbs and for the quantitative assessment of any known active ingredients (Phillipson, 2007). Several regulatory bodies including Traditional Medicines Boards (TMBs, in Nigeria and other African Countries), Medicines and Healthcare products Regulatory Agency (MHRA), Herbal Medicines Advisory Committee (HMAC) (Uk), American Herbal Products Association (AHPA) and several other pharmacopoeia (British, Chinese, German, Japanese) provide guidelines and advice on the safety, quality and utilization of the plant herbal products in several countries (Yadav and Dixit, 2008). Scientific research communities are currently engaged in phytochemical research, and pharmacognosy, phytomedicine or traditional medicine are various disciplines in higher institutions of learning that deals specifically with research in herbal medicines. It is estimated that > 5000 individual phytochemicals have been identified in fruits, vegetables, and grains, but a large percentage still remain unknown and need to be identified before we can fully understand the health benefits of phytochemicals (Liu, 2004).

Despite the increased interest in medicinal plant research worldwide, only rare (Voravuthikunchai et al., 2005) or no publications are found even in the developed countries on efficacy of these plants on verocytotoxic bacteria. Though there are several published data on the efficacy of phytochemicals on *Escherichia coli* and *Shigella* spp, and other gram- negative bacteria, and antibiotic resistant bacteria (Nascimento et al., 2000; Yagoub, 2008; Okigbo et al., 2009; El-Mahmood, 2009;

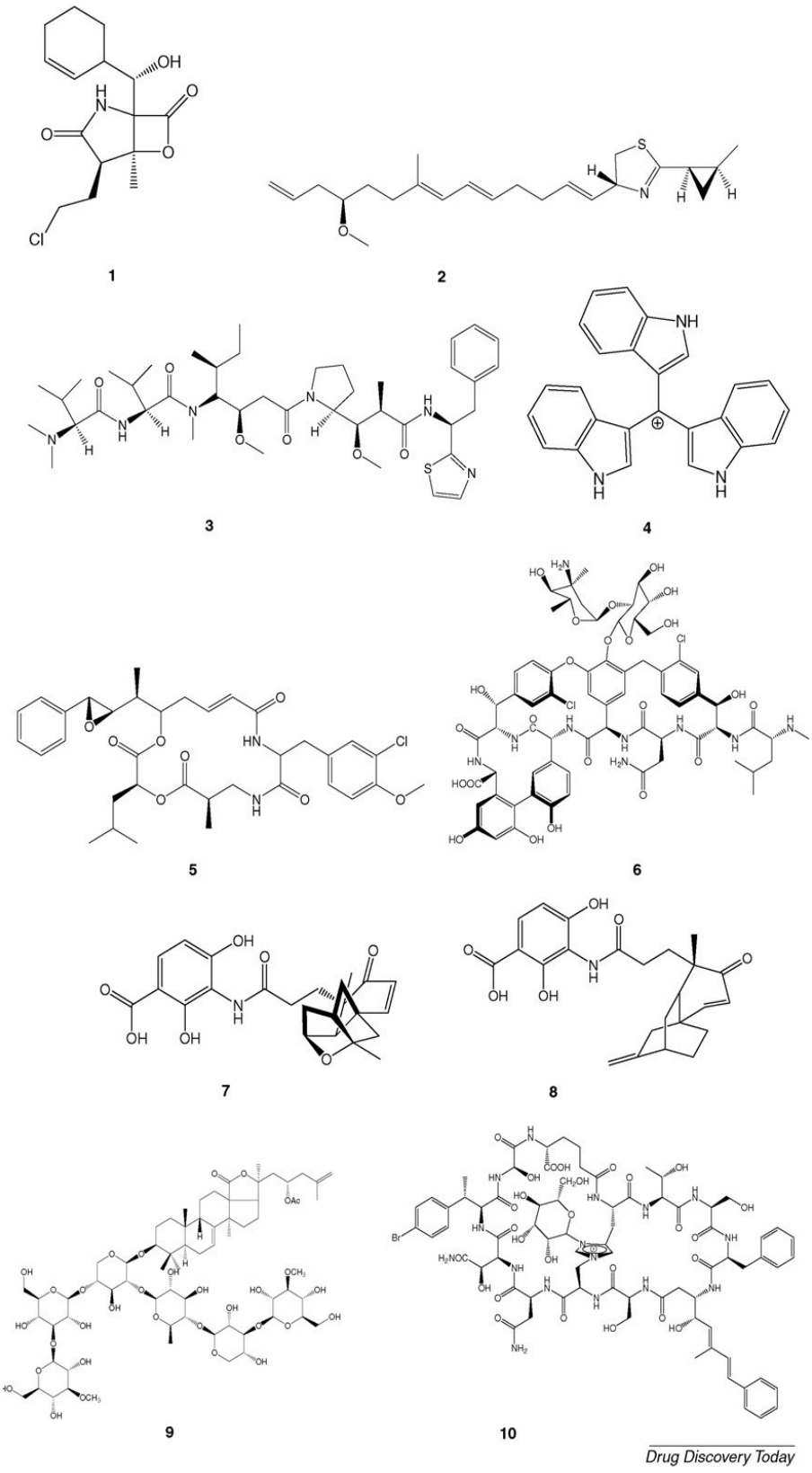

Figure 1. Natural products – recently discovered and/or in development. **(1)** Salinosporamide A; **(2)** curacin A; **(3)** dolastatin 10; **(4)** turbomycin A; **(5)** cryptophicin; **(6)** vancomycin; **(7)** platensimycin; **(8)** platencin; **(9)** stichloroside; **(10)** theopalauamide (Source; Harvey, 2008).

Aiyegoro et al., 2009), relatively none is available on efficacy of these plants on the verocytotoxin producing *Escherichia coli* 057: H7 and other related bacteria in Africa to the best of our knowledge. Deliberate research derives should be made by researchers especially in the developing world to stockpile beforehand, relevant potential medicinal plant cure against these bacteria. This should be done with a view to developing novel drugs for the chemotherapy of these emerging pathogens.

CONCLUSION

With the increasing interest and so many promising drug candidates in the current development pipeline that are of natural origin, and with the lessening of technical drawbacks associated with natural product research, there are better opportunities to explore the biological activity of previously inaccessible sources of natural products. Since the increasing acceptance that the chemical diversity of natural products is well suited to provide the core scaffolds for future drugs, there will be further developments in the use of novel natural products and chemical libraries based on natural products in drug discovery campaigns. Such array of antimicrobial substances when discovered will in no doubt provide prospective alternatives for the control of antimicrobial resistant bacteria in addition to emerging verocytotoxygenic ones.

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