Antimicrobial Compounds in Different Botanical Families

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ABSTRACT

The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years. Ethnopharmacologists, botanists, microbiologists, and natural-products chemists are combing the Earth for phytochemicals and "leads" which could be developed for treatment of infectious diseases. While 25 to 50% of current pharmaceuticals are derived from plants, none are used as antimicrobials. Traditional healers have long used plants to prevent or cure infectious conditions; Western medicine is trying to duplicate their successes. Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found in vitro to have antimicrobial properties.

KEYWORDS: *botanical, antimicrobial, medicine, families, secondary metabolites, chemists, drugs, pharmaceuticals.*

Introduction

In vivo and in vitro studies of extracts from the Phytolaccaceae family plants, evaluating antibacterial (8 publications), antifungal (8), anti-Trypanosoma (2), anti-Leishmania (2), antiviral (1), and antiamoebic (1) activities, are included. The plant species identified belong to genera *Petiveria, Phytolacca, Gallesia, Trichostigma,* and *Seguieria.* The risk of bias in the 22 publications both in vitro and in vitro was suboptimal. The evidence obtained showed that the Phytolaccaceae family, a source of plants with antimicrobial action, can serve as a basis for the creation of new herbal medicines, expanding the possibility of treatment for infectious diseases[1][2] and stimulating their preservation and biodiversity. However, more high-quality studies are needed to establish the clinical efficacy of the plant. Antibacterial activity is found in 51 of 79 vascular plant orders throughout the phylogenetic tree. Most are reported within eudicots, with the bulk of species being asterids.[3][4]Antibacterial activity is not prominent in monocotyledons. Phylogenetic distribution strongly supports the concept of chemical evolution across plant clades, especially in more derived eudicot families[5][6]. The Lamiaceae, Fabaceae and Asteraceae were the most represented plant families, while *Cinnamomum verum, Rosmarinus vulgaris* and *Thymus vulgaris* were the most studied species. South Africa was the most represented site of plant collection. Crude extraction in methanol was the most represented type of extraction and leaves were the main plant tissue investigated. Finally, *Staphylococcus aureus* was the most targeted pathogenic bacteria in these studies.[7][8] Plants have been used for thousands of years by humans to treat various ailments, including bacterial infections.

Many ancestral medicinal uses have been scientifically corroborated using modern techniques that have allowed the identification of active compounds and the characterization of their antibacterial mechanism of action. Some of the compounds of plant origin that have been most studied in recent years are complex plant extracts and essential oils as well as pure compounds such as terpenoids, polyphenols and alkaloids. It should be noted that polyphenols are very chemically diverse and as a group can be subdivided into the following families according to their chemical structures: flavonoids, stilbenes, lignans, tannins and phenolic acids, among others. [9][10]

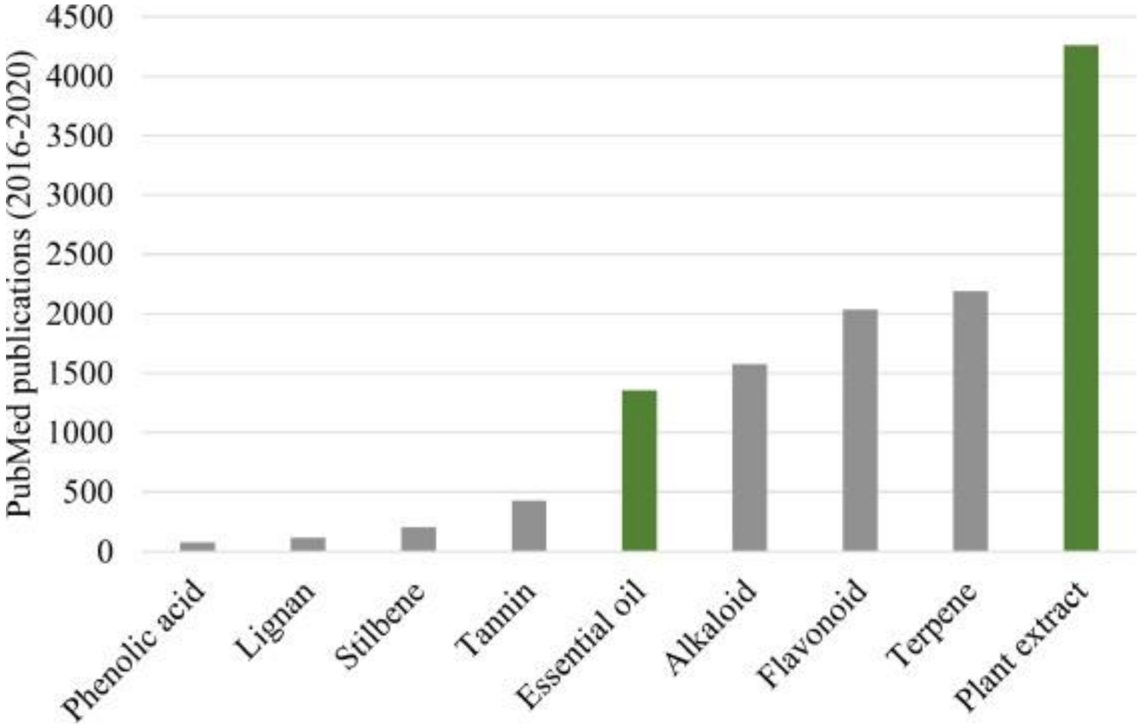

Fig. 1. Antibacterial activity for each group of compounds of plant origin.

Phytochemicals are nonnutritive plant components that confer organoleptic properties and serve as antimicrobial agents. The concentration, composition, structure, and functional groups serve an important role in determining antimicrobial activity. Phenolic compounds are generally the most effective [7]. Based on their chemical structures, they may be divided into different categories including simple phenolic compounds, flavonoids, quinones, tannins, and coumarins. The most important phytochemicals used as food preservatives are essential oils, which have been used by humans across the continents since ancient times. Some alkaloids from plants have also been used as antimicrobials in food. [11][12]Recently, many different phytochemicals have been listed by Negi [8] and their antibacterial activities have been summarized. The antifungal and antifungal toxin activities from various plant extracts including phenolic compounds and essential oils have also been recently reviewed [9]. Polyphenolic compounds from fruits such as cranberry, pomegranate, blueberry, raspberry, and grape were also summarized in 2014 for their antiviral activities against human enteric viruses [4]. Flavones are phenolic compounds with one carbonyl. Flavonols are phenolic compounds with a carbonyl and a 3-hydroxyl group. Flavonoids are hydroxylated phenolic structures with a C3–C6 aromatic ring linkage. They are effective against many microorganisms because of their ability to bind to and inactivate proteins and to complex with bacterial cell walls.[13][14] Catechins provide the antimicrobial activity in oolong teas. The green tea polyphenol, epigallocatechin-3-gallate, was shown to be antiviral against hepatitis B virus replication *in vitro* [2]. Unlike simple phenolic compounds, the degree of hydroxylation does not predict the level of toxicity to microorganisms [1].

Tannins are polymeric phenolic substances that are divided into hydrolysable and condensed tannins (also known as proanthocyanidins). The latter are based on flavonoid monomers and hydrolysable tannins are based on gallic acid. Tannins may be formed by polymerization of quinones or by condensation of flavan derivatives. Their antimicrobial mode of action is similar to that of quinones and they have been shown to be toxic to bacteria, yeasts, and some fungi [1]. Tannins naturally occur in many fruits, nuts, and seeds. A recent review by Lipińska et al. [4] shows that the hydrolysable ellagitannins[15][16] found in pomegranate, strawberry, blackberry, raspberry, walnuts, almonds, and seeds exhibit antimicrobial activity against fungi, viruses, and, importantly, bacteria, including antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA). Additionally, a recent article has comprehensively reviewed the antimicrobial activities of bioactive components from berries including flavonoids (anthocyanins, flavonols, and catechins), phenolic acids, stilbenes, and tannins [5].

Coumarins are phenolic structures comprised of a fused benzene and alpha-pyrone ring. Although toxic to some animals, they have been shown to have species-dependent metabolism, with toxic coumarin derivatives excreted in human urine[17] without adverse health effects. A recent review summarizes not only the anti-inflammatory, anticoagulant, anticancer, antihypertensive, antitubercular, anticonvulsant, antiadipogenic, antihyperglycemic, antioxidant, and neuroprotective properties of coumarins but also their antibacterial, antifungal, and antiviral activities [6].

Clove buds yield approximately 15% to 20% of a volatile oil that is responsible for the characteristic smell and flavor. The bud also contains a tannin complex, a gum and resin, and a number of glucosides of sterols. The principal constituent of distilled clove bud oil (60% to 90%) is eugenol (4-allyl-2-methoxyphenol). The oil also contains about 10% acetyleugenol and small quantities of gallic acid, sesquiterpenes, furfural, vanillin, and methyl-n-amyl ketone. Other constituents include flavonoids, carbohydrates, lipids, oleanolic acid, rhamnetin, and vitamins.[18][19]

Discussion

The essential oil of cinnamon is primarily composed of 65% to 80% cinnamaldehyde and lesser amounts of other phenols and terpenes, including eugenol, trans-cinnamic acid, hydroxycinnamaldehyde, o-methoxycinnamaldehyde, cinnamyl alcohol and its acetate, limonene, α-terpineol, tannins, mucilage, oligomeric procyanidins, and trace amounts of coumarin. Differing material origins and extraction techniques are reported to alter the chemical composition of the extracts, and hence may impact the intended medicinal (and experimental) effects. Nutmeg seeds contain 20% to 40% of a fixed oil, commonly called nutmeg butter. This oil contains myristic acid, trymiristin, and glycerides of lauric, tridecanoic, stearic, and palmitic acids.[20][21]

Nutmeg also yields 8% to 15% of an essential oil that is believed to be partially responsible for the effects associated with nutmeg intoxication. The essential oil contains myristicin, elemicin, eugenol, and safrole. The essential oils of nutmeg and mace are very similar in chemical composition and aroma, with wide color differences (brilliant orange to pale yellow).[22][23] Mace oil appears to have a higher myristicin content than nutmeg oil.

Also present in the oil are sabinene, cymene alpha-thujene, gamma-terpinene, and monoterpene alcohols in smaller amounts. Phenolic compounds found in nutmeg are reported to have antioxidant properties. Other isolated compounds include the resorcinols malabaricone B and malabaricone C, as well as lignans and neolignans. Oregano contains oleanolic and ursolic acids, flavonoids and hydroquinones, caffeic, rosemarinic, and lithospermic acid, tannins, and phenolic glycosides. Phenolic compounds represent 71% of the total oil. The polar phenols thymol and carvacrol are responsible for many of the properties of the essential oil, as well as p-cymene and terpinene. The volatile oils of oregano have demonstrated in vitro antibacterial activity against a wide range of gram-positive and gram-negative microorganisms including *Listeria, Pseudomonas, Proteus*, *Salmonella*, and *Clostridium* species, as well as some methicillin-resistant *Staphylococci*. Low to moderate activity against *Helicobacter pylori* has been reported. Oregano oil appears to inhibit organisms at relatively low concentrations, and its activity could be due to the phenolic components thymol and carvacrol.[24][25]

Onions contain 89% water, 1.5% protein, and vitamins, including B_1, B_2, and C, along with potassium. Polysaccharides such as fructosans, saccharose, and others are also present, as are peptides, flavonoids, and essential oil. Onion contains alliin and similar sulfur compounds, including allylalliin and methyl and propyl compounds of cysteine sulfoxide. Sulfur and other compounds of *A. cepa* have been analyzed. Prostaglandins also have been identified in onion. Onion has reported antibacterial, antiparasitic, and antifungal actions. Growth of oral pathogenic bacteria, including *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Prevotella intermedia*, organisms associated with dental caries and periodontitis, was prevented by onion extracts. Onion juice or oil also have inhibited growth of other gram-positive bacteria and gram-negative bacteria such as *Klebsiella pneumoniae*. Antifungal actions of onion include inhibition of yeasts and a number of molds. The antibacterial, antiparasitic, and antifungal actions of onion is believed to be due to a number of sulfur containing compounds such as alliin, allylalliin, diallyl disulfide and the methyl and propyl compounds of cysteine sulfoxide.Onions are also noted for their ability to make you cry. This effect is due to one of these propyl sulfoxides which is converted to propanethial-S-oxide which then escapes from the onion in vapor form and hydrolyzes to sulfuric acid when it reacts with moisture, causing the familiar eye irritation and lacrimation.[26][27]

Fresh garlic is a source of numerous vitamins, minerals, and trace elements, although most are only found in minute quantities. Garlic contains the highest sulfur content of any member of the genus *Allium*. Two trace elements, germanium and selenium, are found in detectable quantities and have been postulated to play a role in the herb's antitumor effect.

Garlic contains about 0.5% of a volatile oil composed of sulfur-containing compounds (diallyldisulfide, diallyltrisulfide, methylallyltrisulfide). The bulbs contain an odorless, colorless, sulfur-containing amino acid called alliin (S-allyl-L-cysteine sulfoxide), which has no known pharmacologic activity. When the bulb is ground, the enzyme allinase is released, resulting in the conversion of alliin to 2-propenesulfenic acid, which dimerizes to form allicin. Allicin gives the pungent characteristic odor to crushed garlic and is believed to be responsible for some of the pharmacologic activity of the plant.

The antiseptic and antibacterial properties of garlic have been known for centuries. As recently as World War II, garlic extracts were used to disinfect wounds. During the 1800s, physicians routinely prescribed garlic inhalation for the treatment of tuberculosis.

Garlic extracts inhibit the growth of numerous strains of *Mycobacterium*, but at concentrations that may be difficult to achieve in human tissues. Preparations containing garlic extracts are used widely in Russia and Japan. Both gram-positive and gram-negative organisms are inhibited in vitro by garlic extracts. The potency of garlic is such that 1 mg is equivalent to 15 Oxford units of penicillin, making garlic about 1% as active as penicillin.[28]

Garlic extracts have shown antifungal activity when tested in vitro and their use has been suggested in the treatment of oral and vaginal candidiasis. In an attempt to quantitate the in vivo activity of garlic extracts, one research group administered 25 mL of fresh garlic extract orally to volunteers. Serum and urine samples were tested for antifungal activity against 15 species of fungal pathogens. While serum exhibited anticandidal and anticryptococcal activity within 30 minutes after ingestion, no biological activity was found in urine. The findings suggest that while garlic extracts may exhibit some antifungal activity in vivo, they are probably of limited use in the treatment of systemic infections.

Anise oil (1% to 4%) is obtained by steam distillation of the dried fruits of the herb. The highest quality oils result from anise seeds of ripe umbels in the center of the plant. A major component of the oil is trans-anethole (75% to 90%), responsible for the characteristic taste and smell, as well as for its medicinal properties.

The volatile oil also has related compounds that include estragole (methyl chavicol, 1% to 2%), anise ketone (p-methoxyphenylacetone), and beta caryophyllene. In smaller amounts are anisaldehyde, anisic acid, limonene, alpha-pinene, acetaldehyde, p-cresol, cresol, and myristicin (the psychomimetic compound previously isolated from nutmeg).

Constituents of the whole seed include coumarins, such as umbelliferone, umbelliprenine, bergapten, and scopoletin. Lipids (16%) include fatty acids, beta-amyrin, stigmasterol, and its salts. Flavonoids in aniseed include rutin, isoorientin, and isovitexin. Protein (18%) and carbohydrate (50%) are also present. Terpene hydrocarbons in the plant also have been described.[29]

Anise has been evaluated for its antimicrobial action against gram-negative and gram-positive bacteria and also a few fungi. Anise is used in dentifrices as an antiseptic and in lozenges and cough preparations for its weak antibacterial effects.

Results

The main constituent of sassafras oil is safrole, which chemically is p-allyl-methylenedioxybenzene, which comprises up to 80% of the oil. Volatile oil also contains anethole, pinene apiole, camphor, eugenol and myristicin.

The plant contains less than 0.2% total alkaloids (primarily boldine and its derivatives and reticuline) along with tannins, resins, mucilage and wax. Six alkaloids, aporphine and benzylsoquinoline derivatives, have been found in root bark. Two antimicrobial neolignans, magnolol and its related isomer (isomagnolol), from related species *S. randaiensis* have been isolated. Sassafras has been used as a sudorific agent, a flavoring agent for dentifrices, root beers and tobaccos, and for treatment of eye inflammation. Extracts of the roots and bark have been found to mimic insect juvenile hormone in *Oncopeltus fasciatus*. [23][24] The oil has been applied externally for relief of insect bites and stings and for lice. Other external uses include treatment of rheumatism, gout, sprains, swelling and cutaneous eruptions. A recent report compares safrole (the main constituent from sassafras oil), to indomethacin for anti-inflammatory activity and pain treatment in mice.

The plant has been reported to have antineoplastic activity and to induce cytochrome P-488 and P-450 enzymes. Sassafras is said to be antagonistic to certain alcohol effects. Alcohol extracts of the related *S. randaiense* exhibit antimicrobial and antifungal activity in vitro, and this activity appears to be due to the presence of magnolol and isomagnolol.

Morinda citrifolia fruits contain essential oils with hexoic and octoic acids, paraffin and esters of ethyl and methyl alcohols. Ripe fruit contains n-caproic acid, presumably responsible for its distinctive odor, known to attract insects such as *Drosophilia sechellia*. Fresh plants contain anthraquinones, morindone and alizarin. A new anthraquinone glycoside from morinda heartwood has recently been described. Hawaiian researcher Ralph Heinicke discovered a small plant alkaloid he termed xeronine. Damnacanthal, morindone and alizarin are present in cell suspension cultures.[25][26] *Morinda citrifolia* has been used medicinally for heart remedies, arthritis (by wrapping the leaves around affected joints), headache (local application of leaves on forehead), GI and liver ailments.

Alcoholic extracts of *M. citrifolia* leaves displayed good anthelmintic activity in vitro against the human parasite *Ascaris lumbricoides* . Lyophilized aqueous root extracts of the plant showed central analgesic activity, among other effects, suggesting sedative properties of the plant as well.

American Indians reportedly used wintergreen for treating back pain, rheumatism, fever, headaches, and sore throats. The plant and its oil have been used in traditional medicine as an anodyne, analgesic, carminative, astringent, and topical rubefacient.

Wintergreen oil is obtained by steam distillation of the warmed, water-macerated leaves. It is used interchangeably with sweet birch oil or methyl salicylate for flavoring foods and candies. The highest amount of methyl salicylate typically used in candy flavoring is 0.04%.

Wintergreen berries have been used to make pies. A tea made from the leaves was used as a substitute for black tea, *Camellia sinensis*, during the Revolutionary War. Wintergreen tea has been used to relieve cold symptoms and muscle aches.

Wintergreen oil contains approximately 98% to 100.5% of the methyl ester, methyl salicylate. The plant has little odor or flavor until the methyl salicylate is freed. During steam distillation, the gaultherin (also described as primeveroside or monotropitoside) present in the leaves is enzymatically hydrolyzed to methyl salicylate. The purified methyl salicylate is subsequently obtained through distillation. In addition, the sugars D-glucose and D-xylose are obtained. The yield of oil from the leaves is in the range of 0.5% to 0.8%.[27][28]

It had long been believed that the pungent principles of ginger were also responsible for its pharmacologic activity, and this has been found to be accurate. The characteristic aroma of ginger is due mainly to the presence of zingiberol in the volatile oil.

The major constituents in ginger rhizomes are carbohydrates (50 to 70%), which are present as starch. The concentration of lipids is 3 to 8% and includes free fatty acids (eg, palmitic, oleic, linoleic, linolenic, capric, lauric, myristic), triglycerides, and lecithins. Oleoresin provides 4 to 7.5% of pungent substances as gingerol homologues, shogaol homologues, zingerone, and volatile oils. Volatile oils are present in 1 to 3% concentrations and consist mainly of the sesquiterpenes beta-besabolene and zingiberene; other sesquiterpenes include zingiberol and zingiberenol; numerous monoterpenes are also found. Amino acids, raw fiber, ash, protein, phytosterols, vitamins (ie, nicotinic acid and vitamin A), and minerals are among the other constituents.

Analyses of the oleoresins have resulted in the identification of a class of structurally related cardiotonic compounds called gingerols, which upon dehydration, form shogaols and degrade further to zingerone. [6]-gingerol and [6]-shogaol are the main components however, the pharmacologically active compounds [6]- and [10]-dehydrogingerdione, and [6]- and [10]-gingerdione have also been identified. Human clinical trials have examined ginger's antiemetic effects related to kinetosis (motion sickness), perioperative anesthesia, and hyperemesis gravidarum. However, little is still known regarding its human pharmacology in these settings. Animal studies have described enhanced GI transport as well as anti-5-hydroxytryptamine ($5HT_3$) and possible CNS antiemetic effects.[29]

Ginger has been reported to have weak fungicidal, strong antibacterial, and antihelmintic properties. Active constituents have been shown to inhibit reproduction of *Escherichia coli*, *Proteus* species, *Staphylococci*, *Streptococci*, and *Salmonella* but to stimulate the growth of *Lactobacilli*. In vitro anthelmintic activity has been documented for the volatile oil *of Z. purpureum* and activity has also been reported against parasites, such as *Schistosoma* and *Anisakis*.

The cytotoxic compound zerumbone and its epoxide have been isolated from the rhizomes of *Z. zerumbet*. This plant, also a member of the family Zingiberaceae, has been used traditionally in China as an antineoplastic.[27]

Conclusions

The plant kingdom comprises many species of plants containing substances of medicinal value, which are yet to be explored. A large number of plants are constantly being screened for their possible medicinal value.[12] The use of plant extracts in traditional medicine has been going on from ancient time.[13] Herbalism and folk medicine, both ancient and modern, have been the source of much useful therapy.[14-16] In the recent years, the development of resistance of pathogens against antibiotics has become a difficult issue caused by the indiscriminate use of modern antibiotics.[17-23] Therefore, the demand for new and effective antimicrobial agents with broad spectrum activities from natural sources are increasing day by day. Infectious diseases account for approximately one-half of all deaths in tropical countries. The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years. Ethnopharmacologists, botanists, microbiologists, and natural-products chemists are combing the Earth for phytochemicals and "leads" which could be developed for treatment of infectious diseases. While 25 to 50% of current pharmaceuticals are derived from plants, none are used as antimicrobials. Traditional healers have long used plants to prevent or cure infectious conditions; Western medicine is trying to duplicate their successes.[21-25] Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found in vitro to have antimicrobial properties. In industrialized nations, despite the progress made in the understanding of microbiology and their control, incidents of epidemics due to drug resistant microorganisms and the emergence of hitherto unknown disease-causing microbes, pose enormous public health concerns. Historically, plants have provided a good source of anti-infective agents; emetine, quinine, and berberine remain highly effective instruments in the fight against microbial infections. Phytomedicines derived from plants have shown great promise in the treatment of infectious diseases including opportunistic AIDS infections. Plants containing protoberberines and related alkaloids, picralima-type indole alkaloids and garcinia biflavonones used in traditional African system of medicine, have been found to be active against a wide variety of micro-organisms. The profile of known drugs like *Hydrastis canadensis* (goldenseal), *Garcinia kola* (bitter kola), *Polygonum* sp., *Aframomum melegueta* (grains of paradise) will be used to illustrate the enormous potential of anti-infective agents from higher plants[26-29]

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