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Review Article

Bioactive compounds from *Punica granatum, Curcuma longa* and *Zingiber officinale* and their therapeutic potential

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CONTENTS

Abstract 329
Introduction 329
Biological activities of medicinal plants 330
Punica granatum L. 330
Curcuma longa L. 335
Zingiber officinale Rosc. 338
Conclusions 341
Acknowledgements 341
References 341

Abstract

Plants have been one of the major sources of medicines since the dawn of human civilization. The contribution of plant-derived drugs in modern times is still significant and much interest has been focused on exploiting the wide diversity of medicinal plants in both traditional systems of medicine and modern drug development. In this review, we assess three plants, namely *Punica granatum* L., *Curcuma longa* L. and *Zingiber officinale* Rosc., for their biological activities. Recent trends in phytochemical investigation and study of the pharmacological actions of all *P. granatum* components (juice, seeds, leaf, pericarp) suggest possible clinical application for the treatment and prevention of cancer and other diseases where chronic inflammation is believed to play an essential etiological role. *C. longa* extracts and active constituents have a potential role in the prevention of cancer and the management of infectious and chronic diseases. *Z. officinale* extracts and active constituents have potent antioxidant, antiinflammatory, antimutagenic and antimicrobial activities, and some of them have shown anticancer activity in experimental models of carcinogenesis. *Z. officinale* has also been found to be effective against pregnancy-induced and postoperative nausea and vomiting, and has proved useful for treating motion sickness and arthritis symptoms.

Introduction

Herbs, spices, medicinal plants and their preparations have been used to treat ailments since prehistoric times. The treatment of various diseases using plant-based medicines has remained an integral part of many cultures across the globe. The World Health Organization (WHO) estimates that 80% of the people living in developing countries almost exclusively use traditional medicine. Such medicines, derived directly or indirectly from plants, constitute 25% of the pharmaceutical armamentarium. India has been identified as one of the top 12 mega-diversity centers in the world, with immensely rich medicinal and aromatic plants occurring in diverse ecosystems. These medicinal plants are used both for primary healthcare and for treating chronic diseases such as AIDS, cancer, hepatic and cardiac disorders and age-related diseases such as memory loss, osteoporosis and diabetes. In the Indian coded system, Ayurveda currently uses as many as 1,000 single drugs and over 8,000 compound formulations of recognized merit. Similarly, 600-700 plants are used by other systems, such as Unani, Siddha and Amchi (1).

The use of medicinal plants and other natural products with therapeutic properties is as ancient as human civilization and for centuries natural products were the main source of drugs. About 25% of the drugs prescribed worldwide still come from plants, with 121 such compounds still currently in use. At the beginning of the 21st century, 11% of the 252 drugs considered basic and essential by the WHO were exclusively of flowering plant origin. In recent years, there has been serious rethinking on the use of medicinal plants and traditional medicines as a source of new bioactive compounds for the treatment of various ailments (2-5). This is primarily due to the slow progress in drug development from synthetic and other modern approaches and the acceptance of herbal medicine in both developed and developing countries. Traditional medicinal practices form an integral part of

complementary or alternative medicine. However, their efficacy and mechanism of action have not been tested scientifically in most cases. These single or polyherbal preparations often produce beneficial responses due to their active chemical constituents (6, 7).

The data that have emerged on the biological activities of medicinal plants in the last two decades are impressive, and several plant active constituents are being used in the development of modern herbal medicines or have become part of modern drug therapy. In this article, we have attempted to review the recent progress made on bioactive compounds identified from three traditionally used medicinal plants. The antimicrobial, antioxidant, antimutagenic and anticancer properties of these plant-based compounds are discussed, as well as the ethnomedicinal uses of the plants and their therapeutic potential.

Biological activities of medicinal plants

Medicinal plant extracts and active constituents are known for their multiple biological activities, which are due to the presence of an array of compounds with structural and functional diversity (8). Some of these activities, including antioxidant, antimutagenic and antimicrobial activities, are discussed below.

Antioxidant activity

Free radicals, produced as a result of normal biochemical reactions in the body, are implicated in contributing to cancer, atherosclerosis, aging, immunosuppression, inflammation, ischemic heart disease, diabetes, hair loss and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (7). The human body possesses innate defense mechanisms to counter free radicals in the form of enzymes, such as superoxide dismutase, catalase and glutathione peroxidase. Vitamin C and E, selenium, zinc, β-carotene, lycopene, lutein and other carotenoids have been used as supplementary antioxidants. In addition to these, secondary metabolites of plants such as flavonoids and terpenoids play an important role in the body's defense against free radicals. The relationship between free radicals and disease can be explained by the concept of oxidative stress. Under this situation, the balance between pro-oxidant and antioxidant factors is disturbed, which results in molecular damage to lipids, carbohydrates, proteins and DNA. Thus, an antioxidant may prevent and/or improve different disease states (9). Natural compounds, especially those derived from dietary sources, provide a large number of antioxidants. In addition to dietary sources, various Indian medicinal plants also provide antioxidants (10).

Antimutagenic activity

Mutations are the cause of inborn errors of metabolism, leading to morbidity and mortality in living organisms. Besides inherited metabolic disorders, a spectrum of age-related human diseases, including cancer, are caused by mutations. Mutagenic agents may be synthetic or natural toxic substances. Since cancer has become the number one cause of death in the world (11, 12), much attention has focused on the chemoprevention of cancer, with little success. However, less attention has been given to the substances in medicinal plants and herbal medicines that may serve to protect against chemical mutagens or carcinogens acting as initiators in the carcinogenic process. The chemical substances present in plants may act as antimutagens or anticarcinogens by blocking or trapping ultimate carcinogen electrophiles in a nucleophilic chemical reaction to form innocuous products. A continuous input of these substances could serve as a buffer against DNA damage. A wide array of phenolic substances, particularly those present in dietary and medicinal plants, have been reported to possess substantial antimutagenic and anticarcinogenic activities (12-15). Antiinflammatory, antioxidant, antimutagenic and anticancer activities are closely linked and are sometimes exhibited by the same compound (16-18).

Antimicrobial activity

Exploring the healing power of plants is an ancient concept. For many years, people have tried to alleviate and treat diseases with different plant extracts and formulations (19). The discovery of antibiotics was a great advance in modern medicine, leading to a considerable reduction in morbidity and mortality from infectious diseases. Despite this, widespread overprescribing and inappropriate use of antibiotics have led to the development of resistance in previously susceptible organisms. The development of antibiotic resistance, especially to multiple old- and new-generation antibiotics, has created immense clinical problems in the treatment of infectious diseases caused by both bacteria and fungi. The toxicity of many systemically used antifungal drugs has restricted their application. Many fungi, including *Candida*, have also developed resistance to antifungal drugs. Therefore, antimicrobial compounds with a novel mode of action that are effective against multidrug-resistant bacteria and fungi are needed. Considerable data on the antimicrobial activity of medicinal plants have been generated (20-24), but further work on the characterization of the active constituents and their efficacy *in vivo* and other pharmacological actions is required in order to use this information to enhance the activity of older antibiotics or synergistic interactions among active constituents and reverse drug resistance.

***Punica granatum* L.**

Ethnomedicinal uses

P. granatum L. (Punicaceae) is a native shrub of Asia and Mediterranean Europe. For centuries, the fruits, leaves, flowers and bark of this plant have been used to

ameliorate diseases ranging from conjunctivitis to hematuria (25). In Ayurvedic medicine, the pomegranate is considered “a pharmacy unto itself”. The bark and roots are believed to have anthelmintic properties (26). In Unani medicine, a Middle Eastern traditional medical system that later took root in India, pomegranate flowers serve as a remedy for diabetes. The dried pomegranate peels are decocted in water and used both internally and externally for numerous conditions (27, 28). An extensive survey of ethnomedicinal literature indicated that pomegranate has been used as an anthelmintic, astringent, bactericidal, refrigerant, stimulant, stomachic, hemostatic and hair dye, and to alleviate the symptoms of asthma, bronchitis, cough, cardiac conditions, dysentery, diarrhea, dyspepsia, inflammation, bleeding disorders, hemorrhoids, wounds, ulcers, bruises, sores, mouth lesions, stomatitis, vaginitis, respiratory and urinary tract infections, and as an antipyretic to ameliorate malaria and seasonal fevers (29-31).

Bioactive compounds

A considerable amount of scientific data has been generated on the phytochemistry of pomegranate fruit, juice and other parts of the plant (32). Some of the common chemical constituents are given below.

Seeds: Seed oils contain 80% conjugated octadecatrienoic fatty acids with, *e.g.*, a punicic acid. Other components of oils include triacylglycerol, lignin, sterols, sex steroids, tocopherols, glycolipids (cerebrosides) and phenyl aliphatic glycosides (33-36).

Juice: Pomegranate juice contains common amino acids, sugars, aliphatic organic acids, hydroxybenzoic acids (gallic acid, ellagic acid), caffeic acid, chlorogenic acid, *p*-coumaric acid, anthocyanins (delphinidin), potent antioxidant flavonoids and minerals, etc. (30-38).

Pericarp: The pericarp contains flavonoids, tannins, complex polysaccharides, alkaloids (pelletierine), flavonol glycosides (quercetin, kaempferol), flavone and flavanone glycosides (naringin) (39-44).

Leaf: The leaves have tannins, glycosides of apigenin and many compounds found in the juice (45).

Flowers: Compounds similar to in the peel are also present in flowers (*e.g.*, gallic acid in peel, ursolic acid in seeds), and they also contain maslinic acid and asiatic acid (46).

Biological activities

Pomegranate has been subjected to screening for various biological activities and found to have multiple activities. Some of the bioactive compounds or classes of compounds exhibiting various activities are listed in Table I. The structures of the main active compounds are given in Figure 1.

Table I: Major bioactive compounds from Punica granatum.

Plant part	Class of compound/compound	Biological activity	Ref.
Seed	Conjugated fatty acids (punicic acid)	Anticancer, antiinflammatory	51
Seed	Sterols (daucosterol, campesterol, stigmasterol, β-sitosterol)	Anticancer, antiinflammatory	34
Seed	Sex steroids (17α-estradiol, estrone)	Anticancer, antiinflammatory	34, 154, 155
Juice	Anthocyanins (delphinidin, pelargonidin, cyanidin)	Antioxidant, antimutagenic, anticarcinogenic	37, 53
Juice, pericarp	Flavonoids (catechin, epicatechin, epigallocatechin 3-gallate)	Antioxidant, antimutagenic, antimicrobial, anticancer	54-57, 151
Juice, pericarp	Hydroxycinnamic acids (caffeic acid, chlorogenic acid, *p*-coumaric acid)	Antioxidant, anticancer, antiinflammatory	42, 150
Juice, pericarp, flower, seed	Hydroxybenzoic acids (gallic acid, ellagic acid)	Antioxidant, antimicrobial, anticancer, antiinflammatory	36, 150, 157
Pericarp, leaf, bark, root	Ellagitannins (punicalin, punicalagin)	Antioxidant, antimicrobial, anticancer	37, 39, 48
Flower, seed	Triterpenoids (ursolic acid)	Anticancer, antioxidant, antiinflammatory	4, 158
Flower	Triterpenoids (maslinic acid, asiatic acid)	Antioxidant	156
Pericarp, bark, root	Alkaloids (pelletierine)	Antioxidant, antimutagenic, antimicrobial	152, 153
Pericarp, leaf	Flavone and flavone glycosides (luteolin, apigenin)	Antimicrobial, antioxidant, antimutagenic, anticancer	45
Pericarp, juice	Flavonol glycosides (quercetin, kaempferol)	Antioxidant, antimicrobial, antimutagenic, anticancer	42, 44
Pericarp	Flavanone glycosides (naringin)	Anticancer	74

For structures see Figure 1.

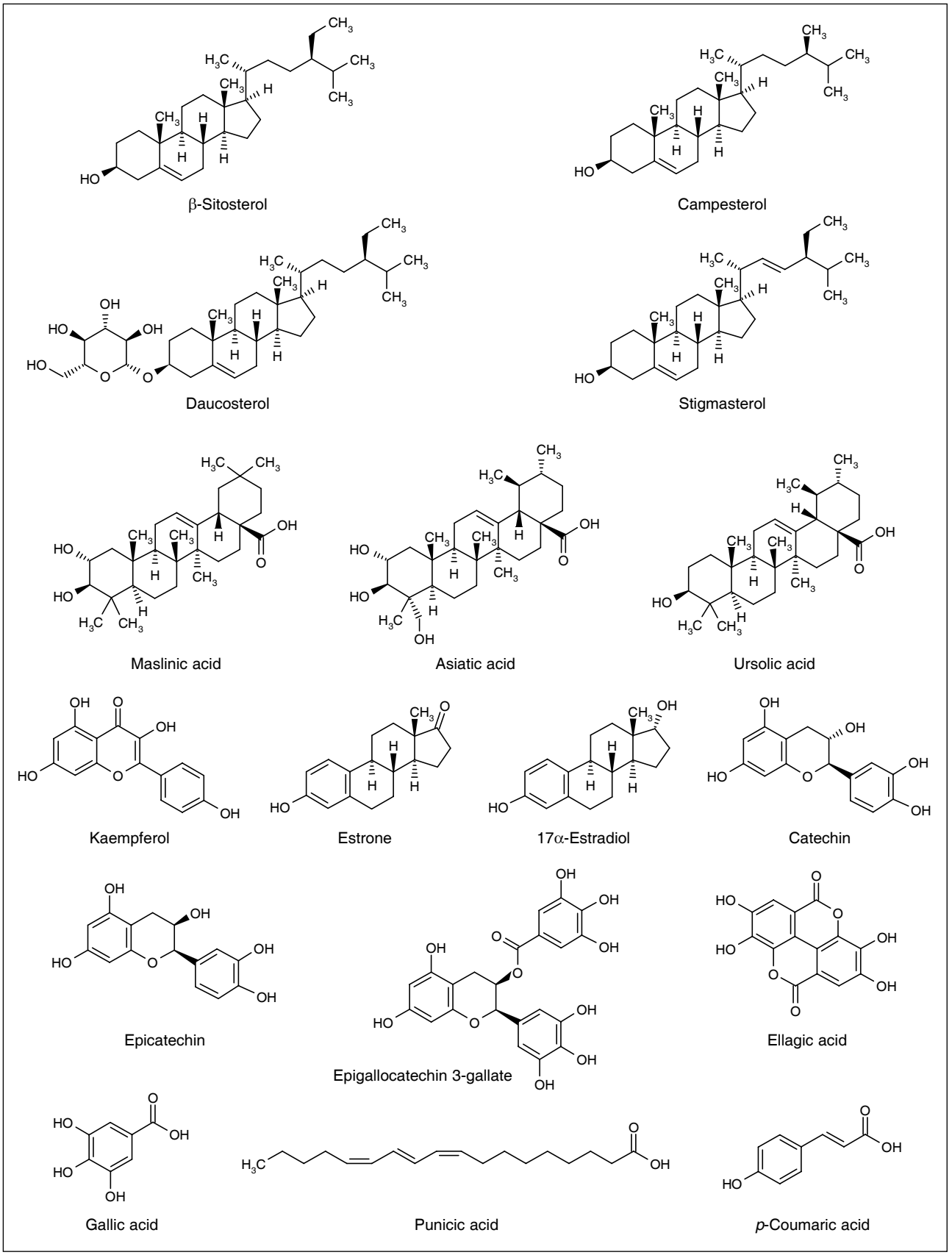

Fig. 1. Bioactive compounds of *Punica granatum* (continued on next page).

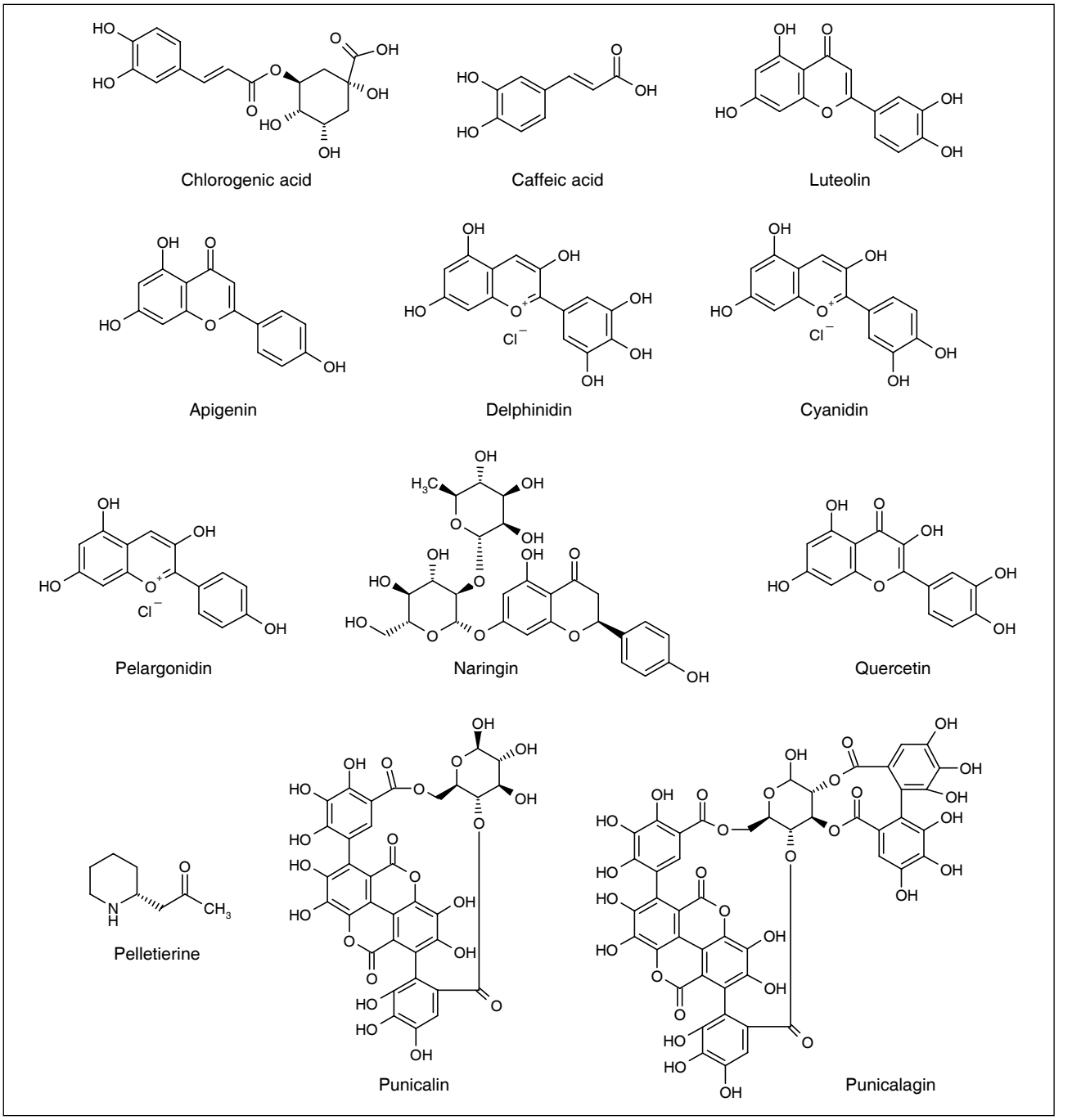

Fig. 1 (Cont.). Bioactive compounds of *Punica granatum*.

1. Antioxidant activity

Antioxidant activities of pomegranate have been described frequently in the last decade. Such reports are mainly based on *in vitro* chemical and biological assays. *In vitro* and many *in vivo* studies described by various researchers have indicated their potential role in the management of various diseases. Due to the chemical complexity of pomegranate and the use of different assays, it is difficult to make comparative analyses of plant extracts and phytocompounds and their relative therapeutic importance. Moreover, since the clinical antioxidant efficacy of pomegranate may be impaired by poor bioavailability of active compounds (47), the strengths and weaknesses of pomegranate need to be considered. The presence of antioxidants has been reported in pomegranate juice (48) and the antiatherogenic effects of pomegranate juice in healthy humans may be due to its antioxidant activity (49).

Antioxidant activity has also been documented for extracts and fractions of pomegranate, including ethyl

acetate and methanol extracts (50), fermented and fresh juices (51), peel and seed extracts (52). Noda *et al*. (43) demonstrated the antioxidant activity of a freeze-dried preparation of a 70% acetone extract and its three major anthocyanidins (delphinidin, cyanidin and pelargonidin). The ID_{50} values for these compounds were 2.4, 22 and 456 μM, respectively. Compounds with antioxidant activity such as gallocatechins and prodelphinidins were also isolated from pomegranate peel (53). The antioxidant activity of pomegranate parts/components follows the order: fresh juice > total pomegranate tannins > punicalagin > ellagic acid (54).

Many studies have assessed the antioxidant potency of pomegranate fruit ellagitannins and anthocyanins in crude extracts or purified fractions (54-56). Reddy *et al.* (57) isolated ellagic acid, gallagic acid, punicalins and punicalagins from pomegranate juice byproducts. These compounds showed no cytotoxicity and exhibited varying degrees of antioxidant activity. Their findings are in contrast with reports of toxicity (liver necrosis) for α- and β-punicalagin in male albino mice (39). The *P. granatum* flower extract possesses potent antioxidant activity and abrogates ferric nitrilotriacetate (Fe-NTA)-induced hepatotoxicity in mice (58). The arils, juice and rinds of *P. granatum* fruits and their aqueous and ethyl acetate extracts displayed good antioxidant activity (59). Surveswaran *et al*. (7) evaluated the antioxidant activity of 133 Indian medicinal plants, including pomegranate leaf and peel extracts, and found that the peel extract showed relatively high antioxidant activity and phenolic contents.

Guo *et al*. (60) investigated the antioxidant activities of three parts (peel, juice and seed) and extracts of three pomegranate varieties in China using a chemiluminescence (CL) method *in vitro*. The scavenging ability of pomegranate extracts (PEs) on superoxide anion, hydroxyl radical and hydrogen peroxide was determined using the pyrogallol luminol, $CuSO_4$-Phen-Vc-H_2O_2 and luminol-H_2O_2 systems, respectively. The DNA damage-preventing effect of PEs was determined using the $CuSO_4$-Phen-Vc-H_2O_2-DNA CL system. The results showed that the peel extract of red pomegranate had the best scavenging effect on superoxide anion, with the lowest IC_{50} value (4.01 ± 0.09 μg/ml) of all PEs. The seed extract of white pomegranate was the most effective in scavenging hydroxyl radical of all nine extracts (IC_{50} = 1.69 ± 0.03 μg/ml). The peel extract of white pomegranate had the best scavenging ability on hydrogen peroxide, showing the lowest IC_{50} value (0.032 ± 0.003 μg/ml) of all nine extracts. The seed extract of white pomegranate (IC_{50} = 3.67 ± 0.03 μg/ml) exhibited the most potent DNA damage-preventing effect of all the PEs. Examples of beneficial *in vivo* and clinical effects due to the antioxidant activity of pomegranate have been well documented (58, 61-63).

2. Antimutagenic and anticancer activity

Extracts of dried pomegranate peels were prepared in ethyl acetate, acetone, methanol and water. The dried extracts were then examined for antioxidant activity by the formation of a phosphomolybdenum complex and for their activity against the mutagenicity of sodium azide in the Ames test. All the peel extracts exhibited marked antioxidant activity, the water extract having the lowest activity. The order of antioxidant activity varied because of differential responses at four concentrations (25, 50, 75 and 100 μg/ml) in each solvent. All the extracts decreased sodium azide mutagenicity against *Salmonella typhimurium* (strains TA100 and TA1535), either strongly or weakly. At 2500 μg/plate all the extracts showed strong antimutagenic activity. The antimutagenic activity of the water extract was the strongest, followed by the acetone, ethanol and methanol extracts. The overall results showed that pomegranate peel extracts have both antioxidant and antimutagenic properties and may be exploited as biopreservatives in food applications and neutraceuticals (64).

Alekperov (65) examined the antimutagenic effect of bioactive compounds from *P. granatum*, *Diospyros kaki*, *Cydonia oblonga* and the roots of *Glycyrrhiza glabra*. The antimutagenic effects of these compounds separately as well as in complex mixtures were studied against mutations induced by genotoxic agents (X-rays, *N*-methylnitrosourea, cyclophosphamide, sodium fluoride [NaF]) and aging in bone marrow cell chromosomes from mice and rats. When tested separately or in a complex mixture, the plant products showed the ability to decrease the frequency of chromosomal aberrations. The antimutagenic properties of the complex mixture were considerably greater than those of the separate components. Greater activity for the mixture was seen when mutagenesis was the result of X-rays and the natural aging process.

The role of pomegranate in cancer prevention and treatment has recently attracted much interest. Compounds from seeds identified as having anticancer or antiinflammatory effects include ursolic acid, sterols such as daucosterol, campestrol, stigmasterol and β-sitosterol, punicic acid, gallic acid, ellagic acid and caffeic acid. Similarly, anticancer compounds from the peel include flavonoids (*e.g.,* kaempferol), flavones (*e.g.*, luteolin) and flavanone glycosides such as naringin. Many other compounds found in the juice and peel of pomegranate, such as catechins and epicatechins, proanthocyanidins and anthocyanidins, quercetin and ellagitannins have been demonstrated to have anticancer activity (Table I, Fig. 1). The above compounds act on different molecular targets to prevent and/or control cancer in experimental models (32).

3. Antimicrobial activity

The antimicrobial activity of pomegranate (peel, leaf and bark) extracts has been investigated by several researchers against both bacteria and fungi. Antibacterial activity against drug-resistant bacteria (methicillin-resistant *Staphylococcus aureus* [MRSA], Gram-negative enteric bacteria), as well as *Mycobacterium,* has been investigated (20, 21, 66-71). Similarly, antifungal activity was found for pomegranate peel against *Candida albicans* and dermatophytes (72, 73). Phytocompounds suspected to have antimicrobial activity are tannins, flavanols, other phenolics and alkaloids. We have demonstrated antibacterial activity against MRSA and

extended-spectrum β-lactamase-producing drug-resistant enteric bacteria for the crude extract and fractions. Phytochemical analysis and TLC bioautography revealed the presence of major active compounds such as phenolics and flavonoids (23, 24). The peel extracts were found to be nontoxic to sheep erythrocytes, as well as in the Ames mutagenicity test. Reddy *et al*. (57) demonstrated antibacterial and antifungal activities for pomegranate extracts and pure compounds such as ellagic acid, gallic acid, punicalin and punicalagin (Fig. 1). All compounds displayed varying degrees of antimicrobial activity against one or more test microorganisms.

Therapeutic potential

Over the past few decades, scientific research has indicated a credible basis for some of the traditional ethnomedicinal uses of pomegranate. Despite the considerable amount of preclinical work indicating efficacy in cancer prevention or therapy with limited toxicity, few well-designed clinical trials investigating the relative anticancer health benefits of pomegranate have been conducted to date. The phytochemistry and pharmacological actions of all *P. granatum* components have suggested a wide range of clinical applications for the treatment and prevention of infectious diseases and cancer or conditions where chronic inflammation plays an essential etiological role (32). Based on other bioactivities, other potential uses of pomegranate-derived products include the treatment of AIDS, cardiovascular protection, for oral hygiene and as an ophthalmic ointment (73-75).

Pomegranate juice as an edible part of pomegranate has impressive health benefits without significant toxicity. However, evaluation of the toxicity of other parts such as tree bark, and to some extent pericarp and seed oil, may be required. Most of the work conducted on pomegranate has mainly focused on its antioxidant and chemopreventive potential. Further studies are needed to explore the molecular targets of bioactive constituents against various diseases.

***Curcuma longa* L.**

Ethnomedicinal uses

C. longa is commonly known as Haldi, turmeric or Indian saffron and belongs to the family Zingiberaceae. It is cultivated mostly in Ceylon, Belgium, Indonesia, France and in many parts of India, especially in Bengal, Tamil Nadu and Andhra Pradesh. *C. longa* is a perennial herb with simple and large leaves. Its tubers, rhizomes and oil have great importance. Its rhizomes are oblong, ovate or cylindrical. Externally the drug is yellowish brown in color, with a characteristic odor and slightly pungent bitter taste. Root scars and annulations are present on the surface of the rhizome (30, 38). Turmeric has a long traditional use in the Chinese and Ayurvedic systems of medicine, particularly as an antiinflammatory agent and for the treatment of flatulence, jaundice, menstrual problems, hematuria, hemorrhage and colic. Turmeric can also be applied topically in poultices to relieve pain and inflammation. In the traditional Ayurvedic system of medicine it has been used in several ways: 1) as an ingredient in the preparation of medicinal oils, ointments and poultices; 2) in diabetes and leprosy; and 3) for stomachache, as a carminative, tonic, laxative, antirheumatic, blood purifier, vermicide, antiseptic and cure for liver ailments. The raw juice is used for gallstones, gallbladder complaints and dental problems. It is also used for sore throat, the common cold, parasitic skin diseases and hemorrhoids (30, 38).

Bioactive compounds

C. longa contains essential oil (5%), alkaloid, starch grains, yellow matter curcumin and other curcuminoids, turmeric oil (5-8%), caproic acid (0.1%) as a free acid and valeric acid (0.1%) as a combined acid. Distillation of oil yields 2% *d*-sabinene, 1% α-phellandrene and 3% cineole from the lower fraction. The middle fraction yields 30.5% zingiberene and the higher fraction shows a mixture of sesquiterpene hydrocarbons and sesquiterpene alcohol (50.5%). The oil contains small amounts of sesquiterpenes, α- and β-pinene, camphor, camphene and curcumenes. Turmeric contains an essential oil called zingiberene. Examination of its chemical composition showed that it contains proteins, carbohydrates and fiber. The mineral and vitamin contents are calcium, phosphorus, iron, carotene, thiamine, niacin, etc. (30, 38, 77, 78).

Biological activities

C. longa extracts and major active compounds have been subjected to extensive *in vitro* and *in vivo* screening for biological activities and found to have multiple activities, including antiinflammatory, antioxidant, hepatoprotective, hypolipidemic, antimicrobial, antiulcer, antitumor, antifertility, antispermatogenic, insect repellant, antiemetic, antivenom and antidepressant activity (79-82). The major bioactive compounds and their structures are given in Table II and Figure 2. Some of the above activities and their therapeutic potential are discussed below.

1. Antioxidant activity

The antioxidant activity of *C. longa* is well known and documented. Curcumin not only exhibits antioxidant and free radical-scavenging properties, but also enhances the activities of other antioxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase. The effect of curcumin on lipid peroxidation has also been studied in various models by several groups. Curcumin is a good antioxidant and inhibits lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates (83). Lipid peroxidation plays a major role in inflammation, heart disease and cancer. The protective effect of curcumin is due to its antioxidant action, trapping of free radicals, formation of complexes with mutagens, modulation of mutagen metabolism by absorbing xenobiotics (84) and inhibition of superactive oxygen species

Table II: Major bioactive compounds from Curcuma longa.

Plant part	Compound	Biological activity	Ref.
Rhizome	Curcumin	Antimicrobial, antioxidant, antimutagenic, anticancer, antiinflammatory	78, 80, 91, 102-105
Rhizome	Curcuminoids (curcumin I, curcumin II, curcumin III)	Antioxidant, antimutagenic, anticancer, antiinflammatory	77, 80, 91, 92, 101
Rhizome	Demethoxycurcumin	Antioxidant, antimutagenic, anticancer	78, 80, 91
Rhizome	Bisdemethoxycurcumin	Antioxidant, antimutagenic, anticancer, antimicrobial	78, 80, 91
Rhizome	Ar-turmerone	Antimutagenic	78
Rhizome	Curlone	Antimutagenic	81
Rhizome	Sodium curcuminate	Antiinflammatory	78

For structures see Figure 2.

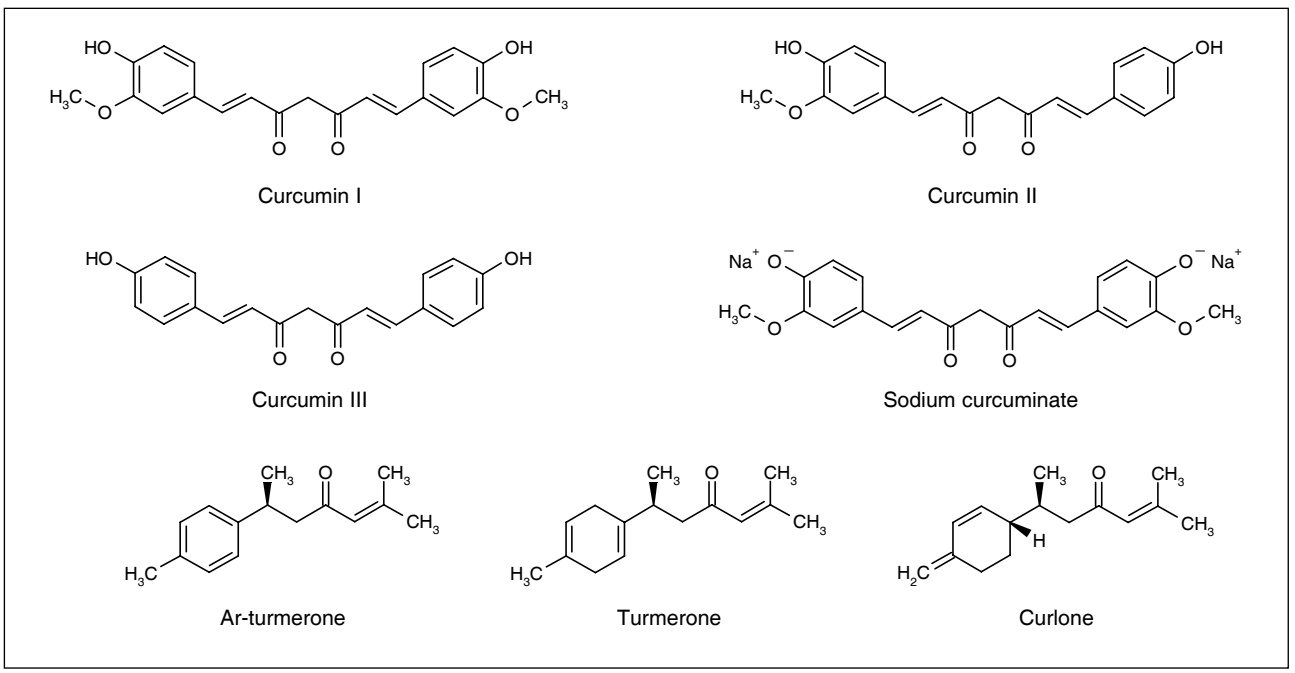

Fig. 2. Bioactive compounds of *Curcuma longa*.

(SOS) functions (85). A chain-breaking or oxidative coupling reaction at the 3'-position of curcumin with the lipid and a subsequent intramolecular Diels-Alder reaction (86) altering the activation and/or detoxification of xenobiotics (87) and the stabilization of the formed phenoxy free radicals are responsible for its free radical-scavenging activity and chemopreventive effect (88-90). Unnikrishnan and Rao (91) studied the antioxidant properties of curcumin and its three derivatives (demethoxycurcumin, bisdemethoxycurcumin and diacetylcurcumin). The authors demonstrated that these substances provide protection of hemoglobin from oxidation at a concentration as low as 0.08 mM, except diacetylcurcumin which has little effect on the nitrite-induced oxidation of hemoglobin.

Turmeric can inhibit lipid peroxidation by maintaining the activities of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase at higher levels. Curcuminoids were found to be potent inhibitors of lipid peroxidation (92) in rat brain homogenates and rat liver microsomes. All of these compounds were more active than the reference drug (α-tocopherol) and curcumin showed better results. In the case of curcumin, the methoxy group appears to play a major role. The phenolic and methoxy groups on the phenyl ring and the 1,3-diketone system appear to be important structural features contributing to these effects. The diketone system is a potent ligand for metals such as iron used in these experiments. Another finding is that the antioxidant activity increases when the phenolic group with a methoxy is at the *ortho* position. The ability of curcumin and its derivatives to protect DNA against $^1O_2$ appears to be related to their structure and may at least partly explain the therapeutic and other beneficial effects of these compounds, including anticarcinogenic and antimutagenic properties (89).

Turmerin constitutes 0.1% of the dry weight of turmeric and is obtained in crystalline form. It is a heat-stable, noncyclic peptide containing 40 amino acid residues, with a blocked *N*-terminus and leucine at the *C*-terminus. It is insensitive to trypsin and pepsin, heat and UV radiation. Turmerin contains three residues of methionine which are partly responsible for the antioxidant activity. Turmerin at 183 nM provided 80% protection against oxidative injury to membranes and DNA. ROS-induced arachidonate release and the mutagenic activity of *tert*-butylhydroperoxide are substantially inhibited by turmerin. Turmerin is noncytotoxic up to milligram concentrations, as seen in the Ames assay and in human lymphocytes (93). Curcuminoids significantly suppress 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative stress via both interference with infiltration of leukocytes into inflamed regions and inhibition of their activation (94).

Curcumin has also been reported to exhibit an inhibitory effect on the lipid peroxidation of linoleic acid induced by air and to inhibit the hemolysis of erythrocytes induced by hydrogen peroxide at low concentrations. Curcumin is a potent inducer of heme oxygenase 1 (HO-1) in vascular endothelial cells and increased heme oxygenase activity is an important component in curcumin-mediated cytoprotection against oxidative stress (95). The turmeric extract preparation and fractions exhibited pronounced antioxidant activity, which was attributed to the presence of curcumin and other polyphenols (96, 97). Maheshwari *et al.* (81) have reviewed the multiple biological activities of curcumin and its potential for preventing cancer.

2. Antimutagenic and anticancer activity

The alcoholic extract of fresh or dried turmeric, its principal components and pyrolyzed turmeric powder and curcumin were tested for mutagenicity using *S. typhimurium* strains with and without metabolic activation. None of the compounds were mutagenic in the test strains (98). Other researchers have found turmeric to be a potent antimutagen against methyl cholanthrene, 4-nitro-*o*-phenylenediamine (NPD), diaminofluorine, urethane (a powerful mutagen) and benzo[*a*]pyrene (BAP) (99). This beneficial effect of turmeric has been postulated to be due to curcumin (83). Natural curcuminoids (curcumin I, II and III) isolated from turmeric were compared for their cytotoxic, antitumor and antioxidant activities. Curcumin III was the most active of the curcuminoids present in turmeric. Synthetic curcumin I and III had similar activity to natural curcumins (77).

The natural curcuminoids curcumin I (diferuloylmethane), curcumin II (feruloyl-*p*-hydroxycinnamoylmethane) and curcumin III (bis-[*p*-hydroxycinnamoyl]-methane) were found to be potent inhibitors of mutagenesis and crotean oil-induced tumor promotion. Curcumin III produced 87.6% inhibition of 2-acetamidofluorene (2-AAF)-induced mutagenesis at a concentration of 100 μg/plate and curcumin II and curcumin I produced 70.5% and 68.3% inhibition, respectively, at the same concentration. Curcumin III was the most effective antimutagenic agent among natural curcuminoids (101).

Curcumin showed a dose-dependent chemopreventive effect in several animal tumor bioassay systems, including models of colon, duodenal, stomach, esophageal and oral carcinogenesis (102, 103). The inhibition of chromosomal damage by curcumin suggests antimutagenic and anticarcinogenic activity (104).

The molecular basis for the anticarcinogenic and chemopreventive effects of curcumin is thought to be its effect on several targets, including transcription factors, growth regulators, apoptotic genes, angiogenesis regulators and cellular signaling molecules. Thus, it is now clear that curcumin acts on multiple targets (81, 105).

3. Antimicrobial activity

The antimicrobial activity of *C. longa* and its constituents is well known. In experimental animal models, turmeric oil (dilution 1:80) was applied dermally on day 7 following the induction of dermatophytosis using *Trichophyton rubrum*. An improvement in lesions was observed in 2-5 days and the lesions disappeared in 6-7 days after the application of turmeric oil (106). The oil fractions were also tested for antifungal activity against *Aspergillus flavus, Aspergillus parasiticus, Fusarium moniliforme* and *Penicillium digitatum* using the spore germination method. Fraction II was found to be the most active. The chemical constituents of turmeric oil, fraction I and fraction II, were determined by gas chromatography and identified by gas chromatography-mass spectrometry. Aromatic turmerone (Ar-turmerone), turmerone and curlone were major compounds present in fraction II, along with other oxygenated compounds (107).

MRSA has emerged worldwide as one of the most important hospital- and community-acquired pathogens. Therefore, new agents are needed to treat MRSA-associated infections. Kim *et al.* (108) investigated the antimicrobial activity of ethyl acetate, methanol and water extracts of *C. longa* L. against MRSA. The ethyl acetate extract of *C. longa* demonstrated greater antibacterial activity than the methanol or water extracts. In the checkerboard test, the ethyl acetate extract of *C. longa* markedly lowered the MICs of ampicillin and oxacillin against MRSA. In the bacterial invasion assay, MRSA intracellular invasion was significantly decreased in the presence of 0.125-2 mg/ml of *C. longa* extract compared to control. These results suggest that the ethyl acetate extract of *C. longa* may have antibacterial activity and the potential to restore the efficacy of β-lactams against MRSA and inhibit MRSA invasion of human macrophages.

Therapeutic potential

Under *in vitro* conditions, curcumin exhibits antiparasitic, antispasmodic, antiinflammatory and gastrointestinal effects and also inhibits carcinogenesis and cancer growth. *In vivo* experiments have demonstrated the antiparasitic and antiinflammatory activity of curcumin and extracts of *C. longa* L. following i.p. and p.o. application in animal models (79, 109-112). Curcumin exhibits

strong antiinflammatory and antioxidant activities and modulated the expression of transcription factors, cell cycle proteins and signal-transducing kinases, prompting mechanism-based studies on the potential of curcumin to prevent or treat cancer and inflammatory diseases (113). Curcumin has been demonstrated to be safe in six human trials and has shown antiinflammatory activity. It may exert its antiinflammatory activity by inhibiting a number of different mediators, such as phospholipases, lipoxygenases, cyclooxygenase type 2 (COX-2), leukotrienes, thromboxanes, prostaglandins, nitric oxide (NO), collagenase, elastase, hyaluronidase, monocyte chemoattractant protein 1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF) and interleukin-12 (IL-12), which play a role in inflammation (111).

Zingiber officinale Rosc.

Ethnomedicinal uses

Z. officinale, commonly known as ginger, is another traditional medicinal plant species belonging to the family Zingiberaceae. It is a perennial and slender rhizomatous herb cultivated throughout India. The major producers of ginger in the world, besides India, are Fiji, Brazil, Africa, China and certain Caribbean islands, the best-quality ginger coming from Jamaica. The edible part of *Z. officinale* is its rhizome. Ginger roots are dried, ground and sprinkled on foods as a spice. The roots are peeled and eaten raw, and also fried, pickled, candied or dipped in chocolate (38). In addition to its culinary functions, it has been used since ancient times for the treatment of colds, fever and loss of appetite. Ginger is an excellent remedy for digestive problems such as flatulence, nausea, indigestion, intestinal infections and certain types of food poisoning. It is also useful for high blood pressure. Ginger inhibits platelet aggregation and may therefore be an ideal condiment for people predisposed to clotting, which may lead to heart attack or stroke (114).

Z. officinale is used chiefly in modern medicine in the form of powders, extracts, distillates, infusions, tinctures and the ethereal *Z. officinale* oil, and is one of the most commonly used herbal supplements in the U.S.A. It is used to prevent the symptoms of travel sickness, but also quite generally as an antiemetic, and it is highly effective for motion and morning sickness. Fresh ginger contains zingibain, which is a protein-digesting enzyme, making it a rich source of digestive enzymes. It has been shown to be effective against vomiting associated with pregnancy and to some extent in the treatment of arthritis (115, 116).

Bioactive compounds

The root of the *Z. officinale* plant is used pharmaceutically; it contains up to 3% of ethereal oil (ginger oil), the chief components of which are sesquiterpene hydrocarbons and sesquiterpene alcohols, primarily zingiberene (30%) and β-bisabolene (10-15%). In addition, it also contains various acrid compounds such as gingerols and shogaols, which are highly effective therapeutically. Ginger oil contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene. The major pungent compounds from the lipophilic rhizome extracts have yielded potentially active gingerols, which can be converted to shogaols, zingerone and paradol. [6]-Gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products. Other compounds such as volatile oils (bisabolene, cineol, phellandrene, citral, borneol, citronellol, geranial, linalool, limonene, zingiberol, zingiberene, camphene), oleoresins (gingerol, shogaol), phenols (gingeol, zingerone), proteolytic enzymes (zingibain), vitamin B_6, vitamin C and linoleic acid have also been reported. The pungency of ginger is due to gingerol. Ginger owes its aroma to about 1-3% of volatile oils, *i.e.,* bisabolene, zingiberene and zingiberol (18, 38, 115).

Biological activities

Z. officinale and its pungent isolated compounds are known to have many potent biological activities, including antiinflammatory, antimicrobial, antimutagenic and chemopreventive properties. Ginger has also been studied for its digestive, hepatoprotective, antiemetic, cardiotonic and other properties both *in vitro* and in preclinical and clinical trials. It is also known for its antiinflammatory effects (117, 118). Some of the bioactive compounds and their structures are presented in Table III and Figure 3. A brief review of its antioxidant, antimutagenic and antimicrobial properties is given below.

1. Antioxidant activity

Ginger is known to have antioxidant activity (119, 120). The nonvolatile fraction of dichloromethane extracts of dried ginger was purified to yield more than 30 compounds, 16 of which were new (121). These compounds were structurally classified into gingerol-related compounds and diarylheptanoids. The pungent components such as gingerol, shogaol and zingerone were found to be highly active. Sekiwa *et al*. (122) have isolated two novel glucosides of 6-gingerdiol from ginger with potential antioxidant activity, namely 1-(4-*O*-β-D-glucopyranosyl-3-methoxyphenyl)-3,5-dihydroxydecane and 5-*O*-β-D-glucopyranosyl-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decane. Of these, the former compound did not show any activity, whereas the latter compound showed strong activity.

Masuda *et al*. (123) have isolated 50 antioxidants from the rhizomes of ginger. These compounds are divided into two groups: gingerol-related compounds and diarylheptanoids. The results suggested that the substituents on the alkyl chain might contribute to both the radical-scavenging effect and the inhibitory effect on auto-oxidation of oils, while inhibitory effects against the 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced peroxidation of liposomes were influenced to some degree by the alkyl chain length; the antioxidant

Table III: Major bioactive compounds from Zingiber officinale.

Plant part	Compound	Biological activity	Ref.
Rhizome	Zingiberene, farnesene	Other activity	114
Rhizome	[6]-Gingerol	Anticancer, antimutagenic	18
Rhizome	[6]-Paradol	Anticancer	18
Rhizome	[6]-Shogaol	Anticancer, antioxidant	18, 120
Rhizome	Zingerone	Antimutagenic	18, 123
Rhizome	[6]-Gingerol and gingerol-related compounds	Anticancer, antioxidant	18, 122

For structures see Figure 3.

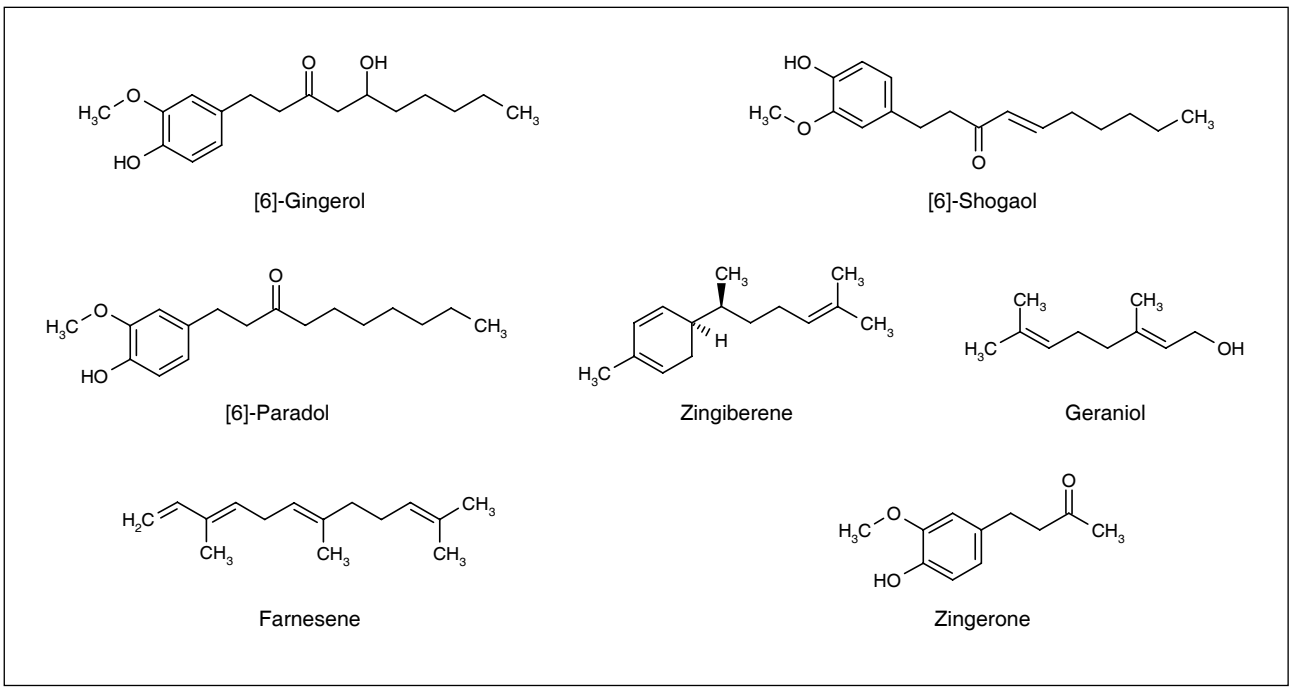

Fig. 3. Bioactive compounds of *Zingiber officinale*.

activity might not be due only to the radical-scavenging activity, but also to their affinity for substrates.

Kuo *et al*. (124) demonstrated the antioxidant and inhibitory activity of *Z. officinale* rhizome-derived materials. The bioactive components of ginger rhizomes were characterized by spectroscopic analysis as zingerone and dehydrozingerone, which exhibited potent antioxidant and tyrosinase-inhibitory activities. Ginger both alone and in combination with α-tocopherol protected the kidney against cisplatin-induced acute renal failure (125).

Siddaraju and Dharmesh (126) reported ginger-free phenolic (GRFP) and ginger-hydrolyzed phenolic (GRHP) fractions of ginger as potent inhibitors of proton potassium ATPase activity (PPA) and *Helicobacter pylori* growth. GRFP and GRHP inhibited PPA with an IC_{50} of 2.9 ± 0.18 and 1.5 ± 0.12 μg/ml, respectively, exhibiting 6-8-fold better potency compared to lansoprazole. GRFP is comprised of syringic (38%), gallic (18%) and cinnamic acids (14%) and GRHP of cinnamic (48%), *p*-coumaric (34%) and caffeic acids (6%) as the major phenolic acids. GRFP and GRHP further exhibited free radical-scavenging activity (IC_{50} = 1.7 ± 0.07 and 2.5 ± 0.16 μg/ml, respectively), inhibition of lipid peroxidation (IC_{50} = 3.6 ± 0.21 and 5.2 ± 0.46 μg/ml, respectively), DNA protection (80% at 4 μg) and reducing power (80-338 U/g), indicating strong antioxidant properties. GRFP and GRHP may therefore be potential inexpensive, multistep antiulcer agents.

2. Antimutagenic and anticancer activity

The active constituents of ginger, shogaol and gingerol, have shown mutagenic activity in the Ames test, whereas zingerone has been shown to concentration-dependently suppress their mutagenic activity (16). Turmeric oil and its fractions also showed antimutagenic activity. Fraction III exhibited maximum antioxidant activity (127). The inhibitory activity of ginger extracts on tumor initiation and promotion is due to pungent vanillyl ketones, including [6]-gingerol and [6]-paradol (17). Gingerol also inhibits the growth of human colorectal can-

cer cells (128) and [6]-gingerol has potent antiangiogenic activity *in vitro* and *in vivo* (129).

Manju and Nalini (130) described the effect of ginger on bacterial enzymes in the 1,2-dimethylhydrazine-induced experimental colon carcinogenesis model. Shukla and Singh (18) have reviewed the antioxidant, antiinflammatory and chemopreventive effects of ginger on experimental carcinogenesis. The anticancer properties of ginger are attributed to the presence of certain pungent vallinoids, *i.e.,* [6]-gingerol and [6]-paradol, as well as some other constituents such as shogaols, zingerone, etc. A number of mechanisms that may be involved in the chemopreventive effects of ginger and its components have been reported from laboratory studies in a wide range of experimental models.

3. Antimicrobial activity

Ginger has been shown to possess broad-spectrum antibacterial and antifungal activities. It significantly inhibits the growth of both Gram-positive and Gram-negative bacteria, including *H. pylori* (131-133). Similarly, antifungal activity against *C. albicans* and other filamentous fungi has also been reported (73). Gupta and Ravishankar (134) performed a comparison of the antimicrobial activity of garlic, ginger, carrot and turmeric pastes against *Escherichia coli* O157:H7 in laboratory buffer and ground beef. The results indicated that the antimicrobial activity of these pastes is decreased in ground beef and laboratory buffer.

Nagoshi *et al*. (135) have found that extracts from the rhizome of *Z. officinale* reduced the MICs of aminoglycosides against vancomycin-resistant enterococci (VRE). The effective compound was isolated and identified as [10]-gingerol. In the presence of [10]-gingerol at one-tenth its MIC, the MIC of arbekacin was lowered. [10]-Gingerol also reduced the MICs of other aminoglycosides, bacitracin and polymixin B, but not of other antimicrobial agents tested. Because [10]-gingerol reduced the MICs of several aminoglycosides in strains both possessing and lacking aminoglycoside-modifying enzymes, it appears that the effect of [10]-gingerol is not related to these enzymes, which mainly confer bacterial resistance against aminoglycosides. It appears that a detergent-like effect of [10]-gingerol potentiated the antimicrobial activity of the aminoglycosides. Since the intrinsic resistance to aminoglycosides against enterococci is due to reduced entry of drugs into the cells, an increase in the membrane permeability caused by [10]-gingerol would enhance the influx of aminoglycosides into enterococcal cells.

Nostro *et al.* (136) have evaluated the effects of extracts (from propolis or *Z. officinale*) combined with clarithromycin against *H. pylori*. The results showed that the combination of propolis extract + clarithromycin and *Z. officinale* extract + clarithromycin exhibited greater inhibition of *H. pylori,* with synergistic or additive effects. Interestingly, the susceptibility to combinations was independent of the clarithromycin susceptibility status. The data demonstrate that combinations of propolis extract + clarithromycin and *Z. officinale* extract + clarithromycin have the potential to control *H. pylori*-associated gastroduodenal disease.

Therapeutic potential

Ginger juice is effective against motion sickness, possibly due to central and peripheral anticholinergic and antihistaminic effects (137). Rheumatoid arthritis symptoms are improved by ginger, with relief of pain, improved joint mobility and decrease in swelling and morning stiffness. The gingerols and shogaols have been shown to possess a cardiotonic action due to a strong positive inotropic effect in animal hearts. They have the ability to reduce platelet aggregation and also have antithrombotic properties. This could be due to inhibition of the production of inflammatory mediators in the prostaglandin and eicosanoid biosynthetic pathways. Gingerol has been shown to increase cardiac function (138-140). The platelet aggregation-inhibitory activity of gingerol is the result of arachidonate metabolism inhibition and secondary inhibition of thromboxane formation (141). The effect of ginger on thromboxane synthetase activity is dose-dependent, or only occurs with fresh ginger, and up to 2 g of dried ginger is unlikely to cause platelet dysfunction when used therapeutically (142).

Results of limited studies in animals with diabetes showed that ginger may reduce sugar and cholesterol levels in blood and lowers blood pressure. However, no human studies with similar results have been reported. A few studies conducted in humans have shown some promise for ginger as a supplement in the treatment of both osteoarthritis and rheumatoid arthritis due to possible antiinflammatory effects. However, mixed results have been found in a limited number of studies of ginger for the treatment of arthritis. Srivastava and Mustafa (144) found that more than 75% of patients receiving 3-7 g of powered ginger daily for 56 days had a significant reduction in pain and swelling associated with either rheumatoid arthritis or osteoarthritis. In clinical trials, ginger has also been shown to be effective in minimizing the effects of motion sickness, with some indication that it may be more effective than dimenhydrinate. The efficacy of ginger has been explained by its ability to neutralize gastrointestinal toxins and acids, thereby slowing feedback from the stomach to nausea centers in the brain (138, 143). Ginger has also been shown to be effective for nausea and vomiting associated with pregnancy and postoperative nausea and vomiting (145, 146). There is less evidence to support its use for motion sickness. Extensive *in vitro* and *in vivo* studies on ginger have led to the speculation that it can be used as an antioxidant, antimicrobial, antineoplastic and antihypertensive agent. However, none of these potential uses have been studied in humans (116).

Adverse effects following the ingestion of ginger are uncommon but can include mild gastrointestinal effects such as heartburn, diarrhea and irritation of the mouth (147). The main compounds in the organic extracts were identified as 6-, 8- and 10-gingerols and 6-, 8- and

10-shogaols. Ginger extracts have potent *in vitro* thromboxane synthetase-inhibitory activity and it is usually suggested that they will therefore interfere with anticoagulant therapy (148). Organic extracts or standards containing gingerols are not cytotoxic, while extracts or standards containing predominantly shogaols are cytotoxic at concentrations above 20 μg/ml (149). The efficacy of ginger has been established in various preclinical and clinical studies in different conditions, which have offered hope for its effective future use in conditions such as digestive disorders, emesis, arthritis/inflammation and platelet aggregation (150). More research analyzing adverse reactions and potential drug interactions, however, needs to be performed.

Conclusions

Based on this review, it can be concluded that *P. granatum* is devoid of toxicity and exhibits various biological activities, notably antioxidant, antiinflammatory, antimicrobial, antimutagenic and anticancer effects. Future clinical trials on active constituents of pomegranate with regard to inflammation and cancer are needed to demonstrate its real therapeutic potential. Considering the vast array of bioactive compounds in pomegranate, further studies on their bioactivities and pharmacological and molecular mode of action are needed.

C. longa and its active constituents have shown multiple biological activities, notably antiinflammatory, antioxidant, anticancer and antimicrobial effects. Curcumin has demonstrated efficacy in angiogenesis (cancer) and in other diseases resulting from oxidative stress. Novel drugs will hopefully be developed by exploiting these properties.

Z. officinale has shown significant efficacy in nausea, vomiting, motion sickness and arthritis, and active compounds with antioxidant, antimutagenic, antimicrobial and anticancer properties have been isolated and require further scrutiny.

Antimicrobially active constituents of the above three plants showed different levels of activity against a variety of pathogenic microorganisms, including multidrug-resistant bacteria. These compounds have not yet been fully exploited for the treatment of infectious diseases alone or in combination with antibacterial or antifungal drugs. Research in this direction is needed to make effective use of these active constituents in the management of infectious diseases.

The therapeutic benefits of these three plants and their active constituents for chronic diseases will require long-term treatment, and orally administered active constituents with improved absorption and bioavailability, stability and no toxicity will be of great value in combating diseases.

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