

Anticancer Activity of Key Lime, *Citrus aurantifolia*

Niththep Narang, Wanee Jiraungkoorskul¹

Mahidol University International College, Mahidol University, Salaya Campus, Nakhon Pathom 73170, ¹Department of Pathobiology, Faculty of Science, Mahidol University, Bangkok 10400, Thailand

ABSTRACT

Citrus aurantifolia (family: Rutaceae) is mainly used in daily consumption, in many cultural cuisines, and in juice production. It is widely used because of its antibacterial, anticancer, antidiabetic, antifungal, anti-hypertensive, anti-inflammation, anti-lipidemia, and antioxidant properties; moreover, it can protect heart, liver, bone, and prevent urinary diseases. Its secondary metabolites are alkaloids, carotenoids, coumarins, essential oils, flavonoids, phenolic acids, and triterpenoids. The other important constituents are apigenin, hesperetin, kaempferol, limonoids, quercetin, naringenin, and rutin, all of these contribute to its remedial properties. The scientific searching platforms were used for publications from 1990 to present. The abstracts and titles were screened, and the full-text articles were selected. The present review is up-to-date of the phytochemical property of *C. aurantifolia* to provide a reference for further study.

Key words: Cancer, *Citrus aurantifolia*, herb, lime, phytochemical substance, plant

INTRODUCTION

Due to the distinct aroma and delicious taste, citrus may be called a miracle fruit that is cultivated worldwide, especially in tropical and subtropical regions.^[1] According to the USDA,^[2] the top lemons and lime producer countries in the world in 2015 were Mexico (2270), Argentina (1450), the EU (1286), the USA (784), Turkey (668), South Africa (330), and Israel (60) in the 1000 metric tons unit. There are many natural metabolites in citrus fruit that potentially provide advantage and good for health.^[3] Products of citrus fruit such as essential oil and pectin of fruit peel are used in the cosmetic^[4] and pharmaceutical industries.^[5,6] Citrus was studied in many countries such as Cameroon,^[7] Iran,^[8] Italy,^[9] Nigeria,^[10] Taiwan,^[11] Thailand,^[12] and Vietnam.^[13] There are many species in the genus of *Citrus*, the most well-known citrus species are *Citrus aurantifolia* (key lime), *C. hystrix* (makrut lime), *C. limonia* (Mandarin lime), *C. limon* (lemon), *C. jambhiri* (rough lemon), *C. sinensis* (sweet orange), *C. aurantium* (sour orange), *C. limetta* (bitter orange), *C. macroptera* (wild orange), *C. tachibana* (tachibana orange), *C. maxima* (shaddock), *C. medica* (citron), *C. nobilis* (tangor), *C. paradise* (grapefruit), *C. reticulata* (tangerine), and *C. tangelo* (tangelo).^[1,14] The present review is up-to-date of the anticancer property of *C. aurantifolia* to provide a reference for further study.

Plant Description

C. aurantifolia is a perennial evergreen tree that can grow to a height of 3–5 m [Figure 1]. Stem: irregularly slender branched and possesses short

and stiff sharp spines or thorns 1 cm or less. Leaves: alternate, elliptical to oval, 4.5–6.5 cm long, and 2.5–4.5 cm wide with small rounded teeth around the edge. Petioles are 1–2 cm long and narrowly winged. Flowers: short and axillary racemes, bearing few flowers which are white and fragrant. Petals are 5, oblong, and 10–12 mm long. Fruits: green, round, 3–5 cm in diameter, it is yellow when rip.^[15,16] All citrus fruits present the same anatomical structures [Figure 2]: (1) flavedo is the external part of the fruit and has a lot of flavonoids as its name. The outer cell wall is composed of wax and cutin for prevention of water loss from the fruit; (2) albedo is the white spongy portion, below the flavedo layer; (3) carpal membranes or septum presenting around 8–11 glandular segments, usually aligned and situated around (4) the soft central core; (5) juice sacs are yellow-green pulp vesicles; and (6) seeds are small, plump, ovoid, pale, and smooth with white embryo.^[17]

Taxonomical Classification

The taxonomy of *C. aurantifolia* is in the kingdom (*Plantae*); subkingdom (*Tracheobionta*); superdivision (*Spermatophyta*); division (*Magnoliophyta*); class (*Magnoliopsida*); subclass (*Rosidae*); order (*Sapindales*); family (*Rutaceae*); genus (*Citrus*); species (*C. aurantifolia*).^[1,14]

Nomenclature

C. aurantifolia is native to the tropical and subtropical regions of Asia and Southeast Asia including India, China, and it was introduced to North Africa, Europe, and worldwide.^[17] The vernacular name of *C. aurantifolia* is also known as lime (English), limah (Arabic), jeruk alit (Bali), zhi qiao (Chinese), lemmetje (Dutch), citronnier (French), limone (German), Kagzi-nimbu (Hindi), jeruk nipis (Indonesia),

Correspondence:

Dr. Wanee Jiraungkoorskul,
Department of Pathobiology, Faculty of Science,
Mahidol University, Bangkok 10400, Thailand.
E-mail: pathobiologymu@gmail.com

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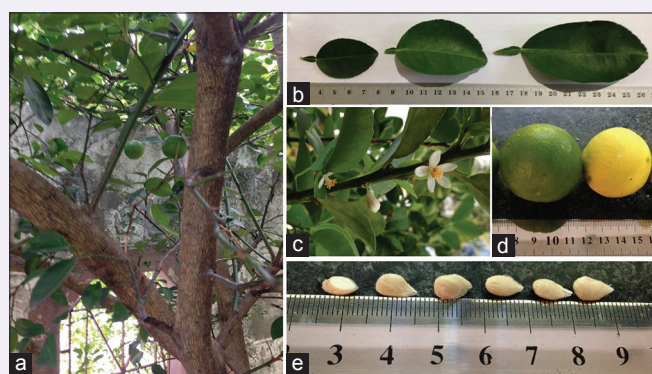


Figure 1: Gross morphology of *Citrus aurantifolia* (a) stems; (b) leaves; (c) white flowers in different stages; (d) ripe yellow and unripe green fruits; and (e) seeds

lima acida (Italian), jeruk pecel (Java), kroch chhmaa muul (Khmer), jeruk neepis (Malay), lamoentsji (The Netherlands), limoo (Persian), dayap (The Philippines), limao galego (Portuguese), lima agria (Spanish), taporo (Tahiti), campalam (Tamil), moli laimi (Tonga), manao (Thai), and chanh ta (Vietnam).^[15]

Phytochemical Substances

C. aurantifolia contains active phytochemical substances as follows: (1) flavonoids including apigenin, hesperetin, kaempferol, nobiletin, quercetin, and rutin,^[18-23] (2) flavones,^[24] (3) flavanones^[25] and naringenin,^[26] (4) triterpenoid,^[27] and (5) limonoids.^[28] In addition, Lota *et al.*^[29] reported at least 62 volatile compounds in the fruit peel oils and 59 in the leaf oils of several lime species. In the fruit peel oils, limonene was the major volatile component, followed by terpinene, pinene, and sabinene. For leaf oils, limonene, pinene, and sabinene were the major components, followed by citronellal, geranial, linalool, and neral. The bioactive compounds from citrus in many countries were reported, for example, Italy: Spadaro *et al.*^[30] reported the fruit essential oils of *C. aurantifolia* as limonene (59%), β -pinene (16%), γ -terpinene (9%), and citral (5%). In the same research group, Costa *et al.*^[9] reported the fruit essential oils of *C. aurantifolia* as limonene (54%), γ -terpinene (17%), β -pinene (13%), terpinolene (1%), α -terpineol (0.5%), and citral (3%). Nigeria: Okwu and Emenike^[31] determined the phytochemical and vitamin contents of five varieties of citrus species; *C. sinensis*, *C. reticulata*, *C. limonum*, *C. aurantifolia*, and *C. grandis*. The presence of bioactive compounds in 100 g of citrus comprise alkaloids (0.4 mg), flavonoids (0.6 mg), phenols (0.4 mg), tannins (0.04 mg), ascorbic acids (62 mg), riboflavin (0.1 mg), thiamin (0.2 mg), and niacin (0.5 mg). Further, the same researchers' group including Okwu and Emenike^[32] also reported that these citrus fruits contains crude protein (18%), crude fiber (8%), carbohydrate (78%), moisture (6%), crude lipid (1%), ash (8%), and food energy content was (363 g/cal) of fresh fruits. The most important minerals detected in the fruit include calcium (3%), phosphorus (0.4%), potassium (1%), magnesium (0.6%), and sodium (0.4%). Lawal *et al.*^[10] reported that the leave essential oil of *C. aurantifolia* contains limonene (45%) and geranial (38%). Taiwan: Wang *et al.*^[11] reported that the chemical substances from citrus fruit contain hesperidin, the major flavanone (6 mg/g), naringin (2 mg/g), diosmin, the major flavone (0.7 mg/g), kaempferol, the major flavanol (1 mg/g), chlorogenic acid, the major phenolic acid (0.1 mg/g), β -cryptoxanthin, the major carotenoid (7 μ g/g), and β -carotene (4 μ g/g), followed by total pectin (87 mg/g). Mexico: Sandoval-Montemayor *et al.*^[33] reported

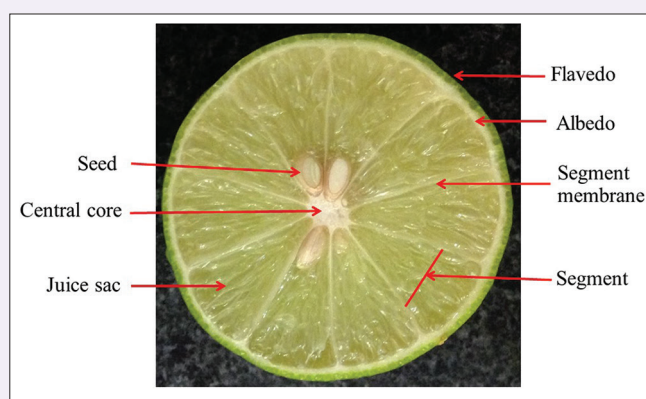


Figure 2: Cross section of *Citrus aurantifolia* fruit

that *C. aurantifolia* fruit peels consist of 44 volatile compounds, for example, dimethoxycoumarin (16%), cyclopentanedione (9%), methoxycyclohexane (8%), corylone (7%), palmitic acid (7%), dimethoxypsoralen (6%), α -terpineol (6%), and umbelliferone (5%).

Traditional Uses

The traditional uses or phytochemical properties of *C. aurantifolia* from several literature reviews are described as antibacterial,^[34-36] antidiabetic,^[37,38] antifungal,^[39-41] antihypertensive,^[42] anti-inflammation,^[7] anti-lipidemia,^[43,44] antioxidant,^[45,46] anti-parasitic,^[47-50] and antiplatelet,^[24] activities. It is used for the treatment of cardiovascular,^[51] hepatic,^[52] osteoporosis,^[53] and urolithiasis^[54,55] diseases and acts as a fertility promoter.^[56] Moreover, it can be used for insecticide activity.^[57,58]

Cancer Incidence

Cancer is a serious public health problem worldwide that is the second leading cause of death, exceeding only by heart disease. A total of 1.6 million new cancer cases and more than five hundred thousand cancer deaths are recorded in the United States in 2015.^[59] The natural products were studied, and it was tried to develop a novel anti-cancer therapy for several years.^[60] The anticancer property of *Citrus aurantifolia* was reviewed in this article for update.

Colon Cancer

Patil *et al.*^[61] reported that *C. aurantifolia* fruit from Texas, USA, consists of at least 22 volatile compounds, and its major compounds were limonene (30%) and dihydrocarvone (31%). About 100 μ g/ml of *C. aurantifolia* extract can inhibit the growth of colon SW-480 cancer cell in 78% after 48 h of exposure. It showed the fragment of DNA and increased level of caspase-3. After a few years, Patil *et al.*^[62] found the new three coumarins from *C. aurantifolia* peel from Texas that were 5-geranyloxy-7-methoxycoumarin, limettin, and isopimpinellin. About 25 μ M of *C. aurantifolia* extract can inhibit the growth of colon SW-480 cancer cell in 67% after 72 h of exposure. The result of apoptosis was confirmed by the expression of tumor suppressor gene casapase-8/3, p53, and Bcl-2, and inhibition of p38 mitogen-activated protein kinases phosphorylation.

Pancreatic Cancer

Patil *et al.*^[63] reported that the active components of *C. aurantifolia* juice contain rutin, neohesperidin, hesperidin, and hesperetin. They also

found limonoid substances such as limonexic acid, isolimonexic acid, and limonin. Moreover, 100 µg/ml of *C. aurantifolia* juice extract can stop 73–89% of pancreatic Panc-28 cancer cells growth after 96 h of exposure. The result of apoptosis was confirmed by the expression of Bax, Bcl-2, casapase-3, and p53. In the next year, Patil *et al.*^[64] reported the five active components of *C. aurantifolia* seeds such as limonin, limonexic acid, isolimonexic acid, β-sitosterol glucoside, and limonin glucoside. They also reported that *C. aurantifolia* extract can stop the growth of pancreatic Panc-28 cancer cells with inhibitory concentration 50% (IC₅₀) of 18–42 µM after 72 h of exposure. Moreover, the order of the induction of apoptosis was isolimonexic acid > limonexic acid > sitosterol glucoside > limonin > limonin glucoside, based on the expression ratio of Bax/Bcl-2.

Breast Cancer

Gharagozloo *et al.*^[65] reported that the 125–500 µg/ml of *C. aurantifolia* fruit juice extract from Iran inhibits the growth of breast MDA-MB-453 cancer cell after 24 h of exposure. Adina *et al.*^[66] reported that the 6 and 15 µg/ml of *C. aurantifolia* peel extract from Indonesia inhibits the growth of breast MCF-7 cancer cell at G1 and G2/M phase, respectively, after 48 h of exposure. The expression of p53 and Bcl-2 was also observed, which indicated the apoptosis.

Lymphoma

Castillo-Herrera *et al.*^[67] reported that the limonin extract from *C. aurantifolia* seed from Mexico inhibits the growth of L5178Y lymphoma cells with IC₅₀ of 8.5–9.0 µg/ml.

Moreover, the citrus secondary metabolites were studied for anticancer activity, for example, flavonoids on skin cancer,^[68] hesperetin on colon cancer,^[69] limonoids on colon cancer,^[70] nobiletin on gastric cancer,^[71] naringenin on prostate cancer,^[72] gastric cancer,^[73] and hepatocarcinoma.^[26]

The information from electronic databases about the protective effect of high citrus fruit intake in the risk of stomach cancer studies until 2007 was reviewed by Bae *et al.*^[74] Li *et al.*^[75] reported the relationship between the citrus consumption and the reduction of cancer incidence among 42,470 Japanese adults, aged 40–79 years, in the Ohsaki National Health Insurance Cohort study from 1995 to 2003. The study revealed a positive relationship that citrus consumption could prevent the occurrence of cancer. Wang *et al.*^[76] reviewed the protective effects of polymethoxyflavones from citrus and proposed that it inhibits carcinogenesis by several pathways in the metastasis, cell mobility, proapoptosis, and angiogenesis.

CONCLUSION

Even though citrus is a common fruit and easy to use in daily consumption, it contains many beneficial substances for human health. It may be a miracle fruit. The phytochemical substances such as alkaloids, carotenoids, coumarins, essential oils, flavonoids, phenolic acids, and triterpenoids exist in citrus abundantly. All of these substances have their board range of pharmacological properties, especially anticancer property. *C. aurantifolia* was studied for its effect against carcinogenesis by mechanisms such as stopping cancer cell mobility in circulatory system; so, inhibiting the metastasis, blocking the angiogenesis, and inducing tumor suppressor gene and apoptosis. The present review suggests that *C. aurantifolia* consumption may have a change to use for cancer therapy.

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Conflicts of interest

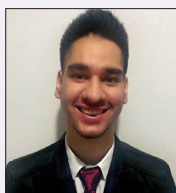
There are no conflicts of interest.

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Nithithev Narang



Wannee Jiraungkoorskul

ABOUT AUTHOR

Nithithev Narang, is currently pursuing his B.Sc. in Biological Sciences (Biomedical concentration) from Mahidol University International College. He plans to graduate by April, 2018. His senior project research paper focuses on the "Comparative evaluation of *in vitro* anthelmintic activity of leaves of *Citrus aurantifolia* and *Citrus hystrix* against *Tubifex tubifex*." It is being carried out under the supervision and guidance of Dr. Wannee Jiraungkoorskul.

Wannee Jiraungkoorskul, is currently working as Assistant Professor in the Department of Pathobiology, Faculty of Science, Mahidol University, Thailand. She received her B.Sc. in Medical Technology, M.Sc. in Physiology, and Ph.D. in Biology. Dr. Wannee Jiraungkoorskul's current research interests are aquatic toxicopathology and efficiency of medicinal herbs.