Isolation and structure elucidation of constituents of *Citrus limon*, *Isodon japonicus*, and *Lansium domesticum* as the cancer prevention agents

Takahiro Matsumoto and Tetsushi Watanabe*

Abstract

In the course of our research to investigate the cancer prevention potency of natural products derived from plant materials, we isolated fifty-five compounds, including twenty-one new compounds from the peels of *Citrus limon*, aerial parts of *Isodon japonicus*, and leaves of *Lansium domesticum*. The chemical structures of the isolated compounds were elucidated by chemical/physicochemical evidence, and nuclear magnetic resonance spectroscopy and mass spectrometry results. Moreover, the absolute stereochemistry of the new compounds were elucidated by various techniques such as chemical synthesis, modified Mosher’s method, Cu-Kα X-ray crystallographic analysis, and comparison of experimental and predicted electronic circular dichroism data. The antimutagenic effects of the isolated and structure-elucidated compounds against heterocyclic amines, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), were evaluated by the Ames test and in vivo micronucleus test. In this review, we present the comprehensive results of the antimutagenic effects of the isolated natural products.

Keywords: *Citrus limon*, *Isodon japonicus*, *Lansium domesticum*, Antimutagenic effects, Ames test, Micronucleus test

Background

Cancer is the leading cause of death worldwide and one of the major risk factors is exposure to the agents that damage the genetic material. These agents are known as genotoxins and, according to their mode of action, are classified into mutagens, carcinogens, or teratogens [1, 2]. Trp-P-1 and PhIP are well known mutagenic and carcinogenic heterocyclic amines that are found in cooked meat. Therefore, it is difficult to completely avoid these risk factors in daily life. On the other hand, previous case-control studies have suggested that the consumption of some plant derived foods such as citrus fruits is associated with a reduced all-cancer incidence [3].

Based on these studies, we searched for antimutagenic materials derived from foods. In the course of this study, we found using the Ames test that the methanolic (MeOH) extracts of *C. limon* [4, 5], aerial parts of *I. japonicus* [6], and leaves of *L. domesticum* [7, 8] showed antimutagenic effects against Trp-P-1 and PhIP. Therefore, we directed our efforts toward the isolation of their constituents and evaluation of the antimutagenic effects of the isolated constituents using the Ames test and in vivo micronucleus test.

Review

Compounds obtained from the peels of *C. limon*

The fruits of *Citrus limon* (L.) Burm.f. contain important natural chemical components, such as flavonoids, furanocoumarins, and limonoids [9]. Previous studies have...
described the biological activities of these compounds, such as the antioxidative, anti-inflammatory, antiallergic, antiviral, antiproliferative, anticarcinogenic, and antimutagenic activities of flavonoids [10], the suppressive effect of limonin on intestinal polyp development in Apc-mutant Min mice [11], and the inhibitory effects of furanocoumarins on human CYP 3A4 [12]. In addition, the essential oil of C. limon leaf has been shown to act as a central nervous system depressant and anticonvulsant in animal models [11].

To investigate the chemical structures of the compounds obtained from the peels of C. limon and their antimutagenic effects, we started the isolation using the MeOH extract obtained by refluxing the fresh peels. The MeOH extract was partitioned into EtOAc (ethyl acetate)- and H2O-soluble fractions and their antimutagenic effects were investigated using the Ames test. The EtOAc- fraction showed the potent antimutagenic effects against Trp-P-1 and PhIP. On the other hand, the H2O-soluble fraction showed no detectable effect. Therefore, the EtOAc-soluble fraction was subjected to normal- and reversed-phase column chromatographies, and finally HPLC to isolate four new coumarins, namely, wakayamalimonol A (1), B (2), C (3), and D (4), a new furanocoumarin wakayamalimonol E (5), two new oxime derivatives limonoximes I (21) and II (22), and 11 known furanocoumarins, (+)-apaensin (6) [13], cnidilin (7) [14], (+)-byakangelicin (8) [15], (-)-byakangelicin (9) [15], (+)-tert-O-methylbyakangelicin (10) [16], (+)-oxyypeucedanin hydrate (11) [17], (+)-tert-O-methoxyypeucedanin hydrate (12) [18], (+)-pangelin (13) [17], (+)-2a,3a-dihydroxyimperatorin (14) [19], (+)-O-methylheraclenol (15) [18], and 8-geranyloxypsoralen (16) [20], a known phenylpropanoid, p-coumaric acid methylester (17), a known sesquiterpene, 4′-dihydrophaseric acid (18) [21], and two limonoids, limonin (19) [22], and nomilin (20) [23] (Fig. 1). The chemical structures of the isolated compounds were elucidated by chemical and physiochemical evidence, including NMR and MS spectra. The absolute stereochemistries of wakayamalimonol A (1) and B (2) were determined by the modified Mosher’s method. In addition, for the identification of the chemical structure and bioassay, wakayamalimonols A (1), B (2) and limonoxime I (21) were synthesized (Scheme 1) [4, 5].

Compounds obtained from the aerial parts of I. japonicus

Isodon japonicus (Burm. f.) H. Hará (Lamiaceae) is a perennial plant with a widely distributed in China and Japan [24]. The aerial parts of I. japonicus have been used as a traditional herbal medicine for the treatment of gastrointestinal disorders, tumors, and inflammatory diseases [25]. Previous reports have described the structures of diterpenoids [26], flavonoids

![Fig. 1 Chemical structures of the constituents isolated from C. limon](image-url)
Scheme 1 Synthesis of wakayamalimonols A (1), B (2) and limonoxime I (21) [4, 5].

Fig. 2 Chemical structures of the constituents isolated from *I. japonicus* [6].
and lignans [28] as constituents of *I. japonicus*. Among them, *ent*-kaurane diterpenoids were the most characteristic constituents of *I. japonicus*. Previously, more than forty *ent*-kaurane diterpenoids were identified in phytochemical studies, and some of these compounds have cytotoxic and antibacterial activities [29]. To evaluate the antimutagenic effects of *ent*-kaurane diterpenoids, we first isolated these compounds and elucidated their structures.

From the MeOH extract of the dried aerial parts of *I. japonicus* (cultivated in Tokushima, Japan), two new *ent*-kaurane diterpenoids, named isodonterpenes I (23) and II (24), together with ten known *ent*-kaurane diterpenoids, oridonin (25) [30], hebeirubescensin H (26) [31], rabdternin F (27) [32], rabdternin E (28) [32], ennein (29) [33], nodosin (30) [34], isodocarpin (31) [35], serrin C (32) [36], isodonal (33) [26], and *ent*-7β,20-epoxy-kaur-16-ene-1β,6α,7α,14a,15a-pentanol-1-O-β-D-glucopyranoside (34) [30], were isolated (Fig. 2). The absolute stereochemistry of isodonterpene I (23) was elucidated by Cu-Kα X-ray crystallographic analysis [6].

Compounds obtained from the leaves of *L. domesticum* *Lansium domesticum* Corr. (Meliaceae), a fruit-bearing tree, grows widely in southeastern Asia [37]. The fruits of this species are edible and are very popular in desserts. Several onoceranoid-type triterpenoids have been isolated from *L. domesticum* peels [38, 39]. Previous reports have described the bioactivities of these onoceranoid-type triterpenoids, such as toxicity against brine shrimp [37], inhibition of leukotriene D4-induced contraction of the guinea pig ileum [40], cytotoxic activity [41], and antibacterial activity against Gram-positive bacteria [42]. However, the bioactivities of these onoceranoid-type triterpenoids have not been investigated thoroughly. Therefore, we attempted to isolate this class of triterpenoids for investigating their biological effects.
From the MeOH extract of *Lansium domesticum* dried leaves, twelve new compounds, namely, lansium acids I (35), II (36), III (37), IV (38), VI (40), VII (41), VIII (42), IX (43), X (44), XI (45), and XII (46) together with nine known compounds, lansiolic acid (47), methyl lansiolate (48) [40], ethyl lansiolate (49) [42], lansioside C (50) [40], lansioside B (51) [40], 8,14-seco-gammacer-7,14-diene-3,21-dione (52) [43], lansionic acid (53) [37], and lamesticumin A (55) [42] were isolated (Fig. 3).

From the MeOH extract of *Lansium domesticum* dried leaves, twelve new compounds, namely, lansium acids I (35), II (36), III (37), IV (38), VI (40), VII (41), VIII (42), IX (43), X (44), XI (45), and XII (46) together with nine known compounds, lansiolic acid (47) [40], methyl lansiolate (48) [40], ethyl lansiolate (49) [42], lansioside C (50) [40], lansioside B (51) [40], 8,14-seco-gammacer-7,14-diene-3,21-dione (52) [43], lansionic acid (53) [37], and lamesticumin A (55) [42] were isolated (Fig. 3).

| Table 1 | Antimutagenic activity of coumarins (1 and 2), limonoids (19 and 20), oxime and synthetic intermediates (21, 21a, and 21b), ent-kaurane diterpenoids (25, 26, 29, 30, and 33), and onoceranoid-type triterpenoids (44, 46–49, 53, and 54) against Trp-P-1 (0.04 μg/plate) using the Ames test [4–8]a |
|---------|---------------------------------------------------------------------------------|
| Inhibition % (Based on number of revertant colonies) | 50 nmol/plate | 100 nmol/plate | 200 nmol/plate | 400 nmol/plate | 800 nmol/plate |
| **Coumarins** | | | | | |
| 1b | 45.8% | 58.7% | 64.6% | 75.6% | 82.3% |
| 2b | 57.8% | 59.8% | 67.1% | 77.2% | 81.4% |
| **Limonoids** | | | | | |
| 19b | 10.7% | 8.0% | 31.0% | 46.0% | 45.8% |
| 20b | 38.7% | 54.9% | 69.8% | 83.1% | |
| **Oxime** | | | | | |
| 21b | 27.3% | 26.2% | 40.5% | 53.7% | 49.0% |
| **Synthetic intermediates of 21** | | | | | |
| 21a b | 22.2% | 20.6% | 21.6% | 0.2% | – |
| 21b b | 31.7% | 39.2% | 51.7% | 54.7% | 61.4% |
| **ent-Kaurane diterpenoids** | | | | | |
| 25b | 34.6% | 57.3% | 53.7% | 65.2% | |
| 26b | 32.9% | 54.4% | 60.9% | 67.8% | |
| 29b | 21.0% | 47.5% | 52.0% | 59.9% | |
| 30b | 46.0% | 56.8% | 72.8% | 73.3% | |
| 33b | 41.0% | 54.9% | 68.3% | | |
| **Onoceranoid-type triterpenoids** | | | | | |
| 44c | 11% | 25% | 50% | 88% | |
| 46c | 14% | 23% | 41% | 65% | |
| 47c | – | 73.8% | 90.5% | 94.2% | |
| 48c | 0.4% | 29.5% | 64.8% | 77.5% | |
| 49c | 3.7% | 7.9% | 8.7% | 42.6% | |
| 53c | 5.1% | 79.9% | 91.5% | 92.4% | |
| 54c | – | 25.0% | 61.0% | 93.0% | |

Table 1 | Antimutagenic activity of furanocoumarins (11, 12, 14, and 15) against Trp-P-1 (0.04 μg/plate) using the Ames test [4]a |
|---------|---------------------------------------------------------------------------------|
| Inhibition % (Based on number of revertant colonies) | 3.1 nmol/plate | 6.3 nmol/plate | 12.5 nmol/plate | 25 nmol/plate | 50 nmol/plate |
| **Furanocoumarins** | | | | | |
| 11 | 22% | 13.9% | 25.0% | 31.5% | 40.9% |
| 12 | 27.0% | 35.9% | 51.6% | 59.5% | 74.7% |
| 14 | 25.0% | 40.5% | 49.7% | 62.8% | 73.7% |
| 15 | 5.6% | 5.6% | 18.1% | 36.6% | 51.2% |

Table 2 | Antimutagenic activity of furanocoumarins (11, 12, 14, and 15) against Trp-P-1 (0.04 μg/plate) using the Ames test [4]a |
|---------|---------------------------------------------------------------------------------|
| Inhibition % (Based on number of revertant colonies) | 3.1 nmol/plate | 6.3 nmol/plate | 12.5 nmol/plate | 25 nmol/plate | 50 nmol/plate |
| **Furanocoumarins** | | | | | |
| 11 | 22% | 13.9% | 25.0% | 31.5% | 40.9% |
| 12 | 27.0% | 35.9% | 51.6% | 59.5% | 74.7% |
| 14 | 25.0% | 40.5% | 49.7% | 62.8% | 73.7% |
| 15 | 5.6% | 5.6% | 18.1% | 36.6% | 51.2% |

a Nobiletin was used as a reference compound. It showed 56% inhibition at 20 nmol/plate
b Compounds showed no antibacterial activity (< 5.0% inhibition at highest concentration) against the S. typhimurium TA98 strain
c Compounds showed weak antibacterial activity (44: 23.2% inhibition at 400 nmol/plate, 54: 23.0% inhibition at 400 nmol/plate) against the S. typhimurium TA98 strain

From the MeOH extract of *Lansium domesticum* dried leaves, twelve new compounds, namely, lansium acids I (35), II (36), III (37), IV (38), VI (40), VII (41), VIII (42), IX (43), X (44), XI (45), and XII (46) together with nine known compounds, lansiolic acid (47) [40], methyl lansiolate (48) [40], ethyl lansiolate (49) [42], lansioside C (50) [40], lansioside B (51) [40], 8,14-seco-gammacer-7,14-diene-3,21-dione (52) [43], lansionic acid (53) [37], lansic acid (54) [37], and lamesticumin A (55) [42] were isolated (Fig. 3). The absolute stereo structures of the new compounds were...
Evaluation of the antimutagenic effects of isolated compounds using the Ames test

The antimutagenic effects of the isolated compounds were evaluated against Trp-P-1 and PhIP by the Ames test using the *S. typhimurium* TA98 strain (Tables 1, 2, 3 and 4). Trp-P-1 and PhIP are well known mutagenic and carcinogenic heterocyclic amines found in cooked meat. We used nobiletin as the positive control that have been reported to have antimutagenic effects using the Ames test [44]. As shown in Tables 2 and 4, among the compounds isolated from the peels of *C. limon*, furanocoumarins, (+)-tert-O-methyloxypeucedanin hydrate were highly effective against both mutagens.

| Table 3 | Antimutagenic activity of coumarins (1 and 2), limonoids (19 and 20), oxime and synthetic intermediates (21, 21a, and 21b), ent-kaurane diterpenoids (25, 26, 29, 30, and 33), and onoceranoid-type triterpenoids (47–49, 53, and 54) against PhIP (1.0 μg/plate) using the Ames test [4–8] a,b,c |
| --- | --- |
|  | Inhibition % (Based on number of revertant colonies) |
|  | 30 nmol/plate | 100 nmol/plate | 200 nmol/plate | 400 nmol/plate | 800 nmol/plate |
| **Coumarins** | | | | | |
| 1b | 17.5% | 29.1% | 48.4% | 48.6% | 81.4% |
| 2b | 18.2% | 35.4% | 62.2% | 77.6% | 86.3% |
| **Limonoids** | | | | | |
| 19b | 27.0% | 39.0% | 25.5% | 50.3% | 46.7% |
| 20b | 23.6% | 44.2% | 74.9% | 79.8% | |
| **Oxime** | | | | | |
| 21b | 12.2% | 11.1% | 29.7% | 47.1% | 63.7% |
| **Synthetic intermediates of 21** | | | | | |
| 21ab | 8.6% | 7.4% | 0.7% | – | – |
| 21bb | 10.7% | 18.0% | | | 68.1% |
| **ent-Kaurane diterpenoids** | | | | | |
| 25b | 55.8% | 62.8% | 73.7% | 80.7% | |
| 26b | 54.3% | 72.0% | 79.5% | 85.5% | |
| 29b | 24.0% | 43.2% | 62.3% | 74.2% | |
| 30b | 51.0% | 64.8% | 81.4% | 85.5% | |
| 33b | 71.0% | 79.5% | 80.4% | | |
| **Onoceranoid-type triterpenoids** | | | | | |
| 47b | 30.8% | 72.7% | 93.7% | 94.9% | |
| 48b | 14.3% | 33.7% | 54.3% | 74.4% | |
| 49b | 4.1% | 17.2% | 22.5% | 41.0% | |
| 53b | 36.8% | 65.2% | 94.1% | 93.9% | |
| **Synthetic intermediates of 21** | | | | | |
| 21aa | 8.6% | 7.4% | 0.7% | – | – |
| 21bb | 10.7% | 18.0% | | | 68.1% |

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*Note:* Table 3 summarizes the antimutagenic activity of various isolated compounds against Trp-P-1 and PhIP using the Ames test. The data is presented as inhibition percentages based on the number of revertant colonies. The compounds were evaluated at different concentrations to determine their effectiveness. Nobiletin was used as a reference compound, showing 56% inhibition at 20 nmol/plate. Compounds showed no antibacterial activity (< 5.0% inhibition at highest concentration) against *S. typhimurium* TA98 strain. Compound 25b showed weak antibacterial activity (≤ 54% inhibition at 400 nmol/plate) against *S. typhimurium* TA98 strain.

**Table 4 Antimutagenic activity of furanocoumarins (11, 12, 14, and 15) against PhIP (1.0 μg/plate) using the Ames test [4]**

|  | Inhibition % (Based on number of revertant colonies) |
| --- | --- |
|  | 3.1 nmol/plate | 6.3 nmol/plate | 12.5 nmol/plate | 25 nmol/plate | 50 nmol/plate |
| Furanocoumarins | | | | | |
| 11 | 22.0% | 28.0% | 29.7% | 46.3% | 64.0% |
| 12 | 47.0% | 57.7% | 68.5% | 73.4% | 83.4% |
| 14 | 34.0% | 41.7% | 51.7% | 67.6% | 70.1% |
| 15 | 47.1% | 62.1% | 65.3% | 69.6% | 78.7% |

*Note:* Table 4 details the antimutagenic activity of furanocoumarins against PhIP using the Ames test. The data is presented as inhibition percentages based on the number of revertant colonies. No compound showed antibacterial activity (< 5.0% inhibition at highest concentration) against *S. typhimurium* TA98 strain at the tested concentrations.
(12) [inhibition against Trp-P-1: 74.7% at 50 nmol/plate] and (+)-2α,3α-dihydroxyimperatorin (14) [inhibition against Trp-P-1: 73.7% at 50 nmol/plate] showed potent antimutagenic effects. The antimutagenic effects of 12 and 14 were much stronger than that of the reference compound, nobiletin [inhibition against Trp-P-1: 56.0% at 80 nmol/plate]. On the other hand, coumarins (1 and 2), and limonoids (19 and 20) showed weak but dose-dependent antimutagenic effects against Trp-P-1 and PhIP. The oxime (21) and synthetic intermediate (21b) showed antimutagenic effect, but the synthetic intermediate without phenyl group (21a) did not show any effects. These results suggest that a phenyl group is necessary for the antimutagenic effects of this class of compounds [4, 5]. The ent-kaurane diterpenoids (26, 27, 30, 31, and 34) from I. japonicus also showed antimutagenic effects against Trp-P-1 [inhibition against Trp-P-1: 47.4–57.3% at 100 nmol/plate]. While their effects were not stronger than that of nobiletin, our study represented the first evaluation of the antimutagenic activities of ent-kaurane diterpenes [6]. Among the isolated onoceranoid-type triterpenoids, the antimutagenic effects of lansionic acid (47) [inhibition against Trp-P-1: 73.8% at 100 nmol/plate] and lansionic acid (53) [inhibition against Trp-P-1: 79.9% at 100 nmol/plate] against Trp-P-1 were equivalent to that of nobiletin. In addition, interesting structure-activity relationships were suggested. Specifically, the compound with a carboxylic acid moiety (47) showed more potent antimutagenic effects than its analogs with either a methyl ester moiety (48) [inhibition against Trp-P-1: 29.5% at 100 nmol/plate] or ethyl ester moiety (49) [inhibition against Trp-P-1: 7.9% at 100 nmol/plate]. Among the esters, the ethyl ester compound 49 showed weaker effects than the methyl ester 48 [7, 8]. The antibacterial

![Fig. 4 Frequency of MNRETS from peripheral blood of mice treated with mutagen (PhIP (50 mg/kg bw)). Significant difference: *0.01 < P < 0.05; **P < 0.01 (Student’s t test). Each point represents the mean and standard deviation of five mice. a Normal or sample feeds that included limonin (19) at low or high dose (0.02% or 0.04%, w/w) were given ad libitum. b Normal or sample feeds that included lansionic acid (53) at low or high dose (0.03% or 0.06%, w/w) were given ad libitum [4, 8].](Image)
activity of tested compounds against the *S. typhi-
murium* TA98 strain were tested using nutrient
agar containing NaCl and all compounds showed
weak [44: 23.2% inhibition at 400 nmol/plate, 54:
23.0% inhibition at 400 nmol/plate] or no (other
compounds: < 5.0% inhibition at highest concen-
tration in Table 1) antibacterial activities [4–8].

Evaluation of antimutagenic effects of limonin (19) and
lansionic acid (53) using in vivo micronucleus test
To examine the antimutagenic effects of limonin (19) and
lansionic acid (53) in vivo, we conducted a micronucleus
test using the peripheral blood of male ICR mice. These
two compounds were isolated enough amount and are the
major constituents of *C. limon* and *L. domesticum*. The
micronucleus test detects chromosomal damage induced
by genotoxic/carcinogenic compounds, and it has been
used to evaluate antimutagenic agents in vivo. We gave ei-
ther normal feed or sample feed that included the limonin
(19) or lansionic acid (53) at low or high dose. The mouse
tail vein blood (5 μL) was taken prior to the administration
of PhIP, and at 24, 48, and 72 h after administration. As a
result, limonin (19) and lansionic acid (53) significantly
decreased the frequency of micronucleated reticulocytes
(MNRETS) treated with PhIP at 24 h and 48 h after the ad-
ministration (Fig. 4) [4, 7].

Conclusions
In conclusion, twenty-one new compounds and thirty-
four known compounds including coumarins, furano-
coumarins, oximes, ent-kaurane diterpenoids, and
onoceranoid-type triterpenoids were isolated from the
peels of *C. limon*, aerial parts of *I. japonicus*, and
leaves of *L. domesticum*. Among them, furanocouma-
rins showed the strongest antimutagenic effects in the
Ames test. It is important to note that furanocouma-
rins were well known Cytochrome P450 (CYP) 1A2
inhibitors [45], and the mutagenicity of Trp-P-1 and
PhIP depends on their bioactivation by CYP 1A2 [46].
These facts suggest that one of the mechanisms of
the antimutagenic effects of furanocoumarins against
Trp-P-1 and PhIP may be the inhibition of the CYP
1A2 enzyme. In addition, the oral intake of limonin
(19) and lansionic acid (53), which are the major
constituents of *C. limon* and *L. domesticum*, respec-
tively, showed significant antimutagenic effects against
PhIP in the in vivo micronucleus test. These results
suggest that these compounds and plant materials are
likely useful agents for cancer prevention.

Abbreviations
ECD: Electronic circular dichroism; HPLC: high-performance liquid
chromatography; ICR: Institute of Cancer Research; MNRET: micronucleated
reticulocyte; NMR: nuclear magnetic resonance; Trp-P-1: 3-amino-1,4-
dimethyl-SH-pyrido[4,3-b]indole; PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-
blpyridine

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Authors’ contributions
The author(s) read and approved the final manuscript.

Authors’ information
Department of Public Health, Kyoto Pharmaceutical University, Misasagi,
Yamashina-ku, Kyoto 607–8412, Japan.

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