Introduction

Nicotiana tabacum L., well known as tobacco, belongs to the genus Nicotiana of Solanaceae family and originated from the tropical Americas.[1] As one of the most commercially-valued agricultural crops worldwide, N. tabacum creates a lot of tax revenues for government and increases the incomes for farmers. In addition to being raw materials for producing cigarettes, the aerial part of N. tabacum is also used as insecticide, sedative, diaphoretic, anesthetic and emetic agents in Chinese folkloric medicine.[2-5] Previous phytochemical researches on Nicotiana plants led to the discovery of more than 2500 compounds including sesquiterpenoids, diterpenoids, alkaloids, as well as flavonoids.[6-11] Many of them possessed excellent pharmacological activities. For example, (1S,2E,4R,6R,7E,11E)-2,7,11-cembratriene-4,6-diol (α-CBD) and its C-4 epimer (1S,2E,4S,6R,7E,11E)-2,7,11-cembratriene-4,6-diol (β-CBD) show potent neuroprotective activities and have been registered as patent in many countries.[12-19]

Several excellent reviews on various aspects of N. tabacum have been published in the past ten years since 2010.[20-24] Of these, only one has been specifically focused on the chemical constituents and their medicinal applications. In 2017, Jassbi et al. described alkaloids, aromatic compounds, flavonoids, volatiles, sesquiterpenoids, diterpenes alcohols, sugar esters, as well as acyclic hydroxygeranyllinalool diterpene glycosides from different Nicotiana species growing around the globe, emphasizing their bioactivities and functions as they have been determined either in bioassay guided purification approaches or in bioassays with plants, in which the expression of specific biosynthetic genes has been genetically manipulated.[25] Over the past years, more interesting compounds have been identified from the crude extract of N. tabacum. Herein, we offer a systematic review of newly reported compounds from N. tabacum over the past four years covering the literatures from the beginning of 2017 through the end of 2020 and describe their structural diversities and bioactivities.

Literature Search

The literature search was performed using a previously reported method.[25-28] The selection of the original articles was of utmost importance because these papers have a direct impact on the findings and the final results. The present review contains all original articles registered with the target subject in the “All Databases” between 2017 and 2020. The search strategy is described below:

Database: All Databases
Title: (from Nicotiana tabacum) or (of Nicotiana tabacum) Timespan: 2017—2020

It should be noted that this review was preliminarily planned in October, 2020. The studies published or being submitted in the current year might not be indexed in Web of Science in a timely manner. Based on the aforementioned approach, 494 records were finally identified. To the best of our knowledge, these publications can be considered to cover most of the related research. After retrieving the records that were related to the field of natural product chemistry, 12 original articles were indexed over a period of four years from the beginning of 2017 to the end of 2020.

Chemical Constituents

The previous chemical investigations of N. tabacum indicated that 46 isolated compounds could be divided into nine categories: diterpenoids (1—6), sesquiterpenes (7—13), furan-2-carboxylic acids (14—22), flavonoids (23—32), sterols (33—36), 2-arylbensofuran (37, 38), isobenzofuran (39—41), phenylpropanoids (42—45), and aminoglucoside (46). Among them, terpenes and flavonoids were predominant (Figure 1).

Cembranoid is one of the characteristic chemical constituent of N. tabacum featured with four isoprene units in the parent skeleton of a 14-membered ring.[29] These ingredients are present in not only the plants belonging to the genera Nicotiana and Pinus, but also marine organisms (e.g., soft coral).[30] In the continuous searches for active compounds from N. tabacum,
six cembranoid diterpenes 1—6 were obtained by the silica gel and preparative HPLC. Among them, 1, 4 and 6 were reported from the leaves of *N. tabacum* for the first time.\(^{31}\) Notably, 6 represented a novel cembrane-type diterpenoid and flavonoid heterodimer.\(^{32}\)

Besides the above diterpenoids, compounds 7—13 were characterized as seven cadinane-type sesquiterpenes. Among those, compounds 7—9 were three new, while compounds 10—12 were three known compounds isolated from the stems of *N. tabacum*.\(^{33}\) Compound 13 possessed a fused 5/6/5/5/5 ring system, representing a totally new carbon skeleton of a sesquiterpenoid combined with a proposed C6 unit.\(^{34}\)

Over the past four years, the researchers also found a series of furan derivatives from the stems of *N. tabacum*. Compounds 14—22 were isolated and characterized as nine furan-2-carboxylic acids.\(^{35,36}\) These compounds are an important class of secondary metabolites containing a five-membered ring and holding oxygen as heteroatoms, which could be also found naturally in algae and microbe.

Flavonoid is also one of the characteristic chemical constituents of *N. tabacum*. Compounds 23—32 are unambiguously classified in this catalogue.\(^{37-39}\) Among them, compounds 27—30 could be further identified as flavonol derivatives according to the substituent group at C-3, while the others were flavones analogues. Interestingly, the latter was all C-alkylated flavones, which were rare in the extract of *N. tabacum*. Four sterols, compounds 33—36, were also isolated from the EtOAc part of an aqueous 70% acetone extract of the roots and stems of *N. tabacum*, along with the flavones 31 and 32.\(^{39}\)

Both compounds 37 and 38 were identified as two new 2-arylfuranurans derivatives, which were purified from the EtOAc part of an aqueous 95% MeOH extract of the stems of

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**Figure 1** Chemical structures of compounds 1—46 (*means new compounds).
| No. | Name | Classification | Bioactivities | Ref. |
|-----|------|----------------|---------------|------|
| 1* | nicotiadterpene B | diterpenoid | No test | [31] |
| 2 | (1S,2E,4S,6R,7E,10E,12S)-2,7,10-cembratriene-4,6,11-triol | diterpenoid | No test | [31] |
| 3 | (1S,2E,4R,6R,7E,10E,12S)-2,7,10-cembratriene-4,6,11-triol | diterpenoid | No test | [31] |
| 4 | (1S,2E,4S,6R,7E)-4,6,11-inhydroxy-1-isopropyl-4,8-dimethylpentadeca-2,7-dien-12-one | diterpenoid | No test | [31] |
| 5 | (1S,2E,4R,6R,7E,11S,12S)-11,12-epoxy-2,7-cembradiene-4,6-diol | diterpenoid | No test | [31] |
| 6* | nicotabaflavonoidglycoside | diterpenoid | No test | [32] |
| 7* | methyl 4-isopropyl-7-methoxy-6-methylnaphthalene-1-carboxylate | sesquiterpene | Moderate anti-TMV activity, Moderate cytotoxicity | [33] |
| 8* | methyl 2-hydroxy-4-isopropyl-7-methoxy-6-methylnaphthalene-1-carboxylate | sesquiterpene | Potent anti-TMV activity, Moderate cytotoxicity | [33] |
| 9* | methyl 2-hydroxy-6-(hydroxymethyl)-4-isopropyl-7-methoxynaphthalene-1-carboxylate | sesquiterpene | Potent anti-TMV activity, Moderate cytotoxicity | [33] |
| 10 | 2,7-dihydroxy-4-isopropyl-6-methylnaphthalene-1-carboxaldehyde | sesquiterpene | Moderate anti-TMV activity, Moderate cytotoxicity | [33] |
| 11 | lacinilene C | sesquiterpene | Moderate anti-TMV activity, Moderate cytotoxicity | [33] |
| 12 | (1S,4R)-7,8-dihydroxy-11,12-dehydrocalamenene | sesquiterpene | Moderate anti-TMV activity, Moderate cytotoxicity | [33] |
| 13* | nicotin A | sesquiterpene | Moderate anti-inflammatory activity | [34] |
| 14* | 5-(3-hydroxy-5-(hydroxymethyl)-4-methoxyphenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | Moderate anti-TMV activity, Moderate cytotoxicity | [35] |
| 15* | 5-(4-hydroxy-5-methoxy-2-methylphenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | Moderate anti-TMV activity, Moderate cytotoxicity | [35] |
| 16 | methyl 5-(4-hydroxy-2-methoxy-6-methylphenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [35,36] |
| 17 | 5-(2’-hydroxy-6’-methylphenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | No test | [35] |
| 18* | methyl 5-(4-hydroxy-2-methoxy-6-methylphenyl)-3-(hydroxymethyl)furan-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [36] |
| 19* | methyl 5-(2-hydroxy-4-methoxy-5-methylphenyl)-3-(hydroxymethyl)furan-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [36] |
| 20* | methyl 5-(6-hydroxy-4-methoxy-2-methylphenyl)-3-(hydroxymethyl)furan-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [36] |
| 21 | 5-(3-hydroxy-4-methoxy-5-phenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [36] |
| 22 | 5-(4-hydroxy-5-methoxy-2-methylphenyl)-3-methylfuran-2-carboxylic acid | furan-2-carboxylic acid | Moderate MRSA activities, Moderate antioxidant activity | [36] |
| 23* | orientaflavone A | flavonoid | Potent anti-MRSA activities | [37] |
| 24 | tabaflavone A | flavonoid | Potent anti-MRSA activities | [37] |
| 25* | 8-formyl-7-hydroxy-6,4’-dimethoxyflavone | flavonoid | Moderate cytotoxicity | [38] |
| 26 | 8-formyl-4’-hydroxy-6,7-dimethoxyflavone | flavonoid | Moderate cytotoxicity | [38] |
| 27 | (2R,3R)-3,5-dihydroxy-7-methoxyflavanone | flavonoid | Nonsignificant cytotoxicity | [38] |
| 28 | quercetin | flavonoid | Nonsignificant cytotoxicity | [38] |
| 29 | kaempferol | flavonoid | Nonsignificant cytotoxicity | [38] |
| 30 | rutin | flavonoid | Nonsignificant cytotoxicity | [38] |
| 31* | 5,7-dihydroxy-2’-methoxy-6-methyl-flavone | flavonoid | Potent anti-TMV activity | [39] |
| 32* | 5-hydroxy-2’,7-dimethoxy-6-methyl-flavone | flavonoid | Potent anti-TMV activity | [39] |
| 33* | (8R,9S,10R,13S,14S,15S)-15-hydroxy-10,13-dimethyl-6-methylflavone | sterol | Moderate anti-TMV activity, Moderate cytotoxicity | [39] |
| 34 | 11α-hydroxy-6-methylene-androsta-1, 4-diene-3,17-dione | sterol | Moderate anti-TMV activity, Moderate cytotoxicity | [39] |
| 35 | 17β-hydroxy-6-methylflavone-androsta-1,4-diene-3-one | sterol | Moderate anti-TMV activity, Nonsignificant cytotoxicity | [39] |
| 36 | 17β-hydroxy-6-methylene-androsta-1, 4-diene-3,16-dione | sterol | Moderate anti-TMV activity, Nonsignificant cytotoxicity | [39] |
Yunyan 85 (a variety of *N. tabacum*). Compounds 39—41 were characterized as three new isobenzofurans, while compounds 42—45 were four known phenylpropanoids. These seven compounds were directly isolated and identified from the EtOAc part of an aqueous 70% acetone extract of the roots of Yunyan 212 (a variety of *N. tabacum*).

An ongoing investigation of natural anticancer compounds from *N. tabacum* led to the discovery of compound 46, an aminoglucoside. Its limited amount prevented the authors from testing the absolute configuration of the acyclic hydroxyl group.

**Bioactivities**

The bioactivities, along with the names and classifications of these isolated compounds, are shown in Table 1. The findings indicated that anti-tobacco mosaic virus (anti-TMV) activity, cytotoxicity, as well as anti-methicillin-resistant *Staphylococcus aureus* (anti-MRSA) activity, were the main indexes used to assess the bioactivities of these naturally occurring compounds. In this section, compounds with potent bioactivities were deliberately selected, and detailed descriptions were provided as follows.

The anti-TMV activity of compounds 7—12 and 39—45 at the concentration of 20 μM were tested using the half-leaf method. The results showed that compounds 8, 9, 11, 43, and 44 exhibited high anti-TMV activity with inhibition rates of 33.6%, 35.8%, 36.7%, 35.1%, and 33.4%. The inhibition rates are even higher than that of nongenamycin (2% water solution) used as a positive control. The other compounds just showed moderate anti-TMV activities with inhibition rates in the range of 22.6%—28.8%, respectively. Compounds 23 and 24 exhibited good anti-MRSA activity with MIC<sub>90</sub> value of (38±4) and (33±5) μg/mL, respectively. However, the MIC<sub>90</sub> value of the levofloxacin (positive control) was larger than (56±6) μg/mL.

In addition to the above, compounds 1—6 and 17 were not tested for any bioactivity, while the others only showed moderate or nonsignificant bioactivities.

**Conclusions and Perspectives**

This review summarized a total of 46 compounds isolated from *N. tabacum* between the beginning of 2017 and the end of 2020, of which 21 compounds were reported as new compounds and account for about 45.65%. However, as one of another characteristic constituents of *N. tabacum*, the alkaloids have received less attention over the past years. Tobacco alkaloids should be one of the most challenging natural product classes to characterize, not only because of their structurally unique skeletons arising from distinct amino acids but also because of their potential bioactivities. As part of our ongoing investigations of natural antimicrobial and insecticidal lead compounds from *N. tabacum*, tobacco alkaloids will be selected for further chemical study preferentially. The bioactivities of these natural compounds are also discussed. However, it's a pity that no obvious structure-activity relationship was found.

All the original articles were identified by searching the Web of Science database, and we think these papers include most of the recently reported natural compounds from *Nicotiana tabacum*. However, it is unavoidable that a certain number of works might not have been retrieved based on the literature search used to compile this review.

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**Conflict of Interest**

The authors declare no conflict of interest.
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