An Update on Chemical Constituents from *Nicotiana tabacum* L. and Their Bioactivities from 2017 to 2020

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Abstract *Nicotiana tabacum* L., well known as tobacco, could be not only used for raw materials of producing cigarettes, but also as a folk Chinese herbal medicine. This paper offers 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 describes their structural diversities and bioactivities. A total of 46 natural compounds and 42 references were updated and compiles in this review, which may be of interest to pharmacognosists and natural products chemists.

Keywords *Nicotiana*, tobacco, chemical constituent, bioactivities

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 folklore 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 pharmaceutical activities. For example, (1*S*,2*E*,4*R*,6*R*,7*E*,11*E*)-2,7,11-cembratriene-4,6-diol (α -CBD) and its C-4 epimer (1*S*,2*E*,4*S*,6*R*,7*E*,11*E*)-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.^[24] 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-arylbenzofurans (37, 38), isobenzofurans (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*,

Figure 1 Chemical structures of compounds 1–46 (*means new compounds).

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-arylbenzofurans derivatives, which were purified from the EtOAc part of an aqueous 95% MeOH extract of the stems of

Table 1 The names, classification, and biological activities of compounds 1—46

No. ^a	Name	Classification	Bioactivities ^b	Ref.
1*	nicotiadiertene B	diterpenoid	No test	[31]
2	(1 <i>S</i> ,2 <i>E</i> ,4 <i>S</i> ,6 <i>R</i> ,7 <i>E</i> ,10 <i>E</i> ,12 <i>S</i>)-2,7,10-cembratriene-4,6,11-triol	diterpenoid	No test	[31]
3	(1 <i>S</i> ,2 <i>E</i> ,4 <i>R</i> ,6 <i>R</i> ,7 <i>E</i> ,10 <i>E</i> ,12 <i>S</i>)-2,7,10-cembratriene-4,6,11-triol	diterpenoid	No test	[31]
4	(1 <i>S</i> ,2 <i>E</i> ,4 <i>S</i> ,6 <i>R</i> ,7 <i>E</i>)-4,6,11-trihydroxy-1-isopropyl-4,8-dimethylpentadeca-2,7-dien-12-one	diterpenoid	No test	[31]
5	(1 <i>S</i> ,2 <i>E</i> ,4 <i>R</i> ,6 <i>R</i> ,7 <i>E</i> ,11 <i>S</i> ,12 <i>S</i>)-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-carbaldehyde	sesquiterpene	Moderate anti-TMV activity, Moderate cytotoxicity	[33]
11	lacinilene C	sesquiterpene	Potent anti-TMV activity, Moderate cytotoxicity	[33]
12	(1 <i>S</i> ,4 <i>R</i>)-7,8-dihydroxy-11,12-dehydrocalamenene	sesquiterpene	Moderate anti-TMV activity, Moderate cytotoxicity	[33]
13*	nicotabin 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-carboxylate	furan-2-carboxylic acid	Moderate anti-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-carboxylate	furan-2-carboxylic acid	Moderate anti-MRSA activities, Moderate antioxidant activity	[36]
19*	methyl 5-(2-hydroxy-4-methoxy-5-methylphenyl)-3-(hydroxymethyl)furan-2-carboxylate	furan-2-carboxylic acid	Moderate anti-MRSA activities, Moderate antioxidant activity	[36]
20*	methyl 5-(5-hydroxy-4-methoxy-2-methylphenyl)-3-(hydroxymethyl)furan-2-carboxylate	furan-2-carboxylic acid	Moderate anti-MRSA activities, Moderate antioxidant activity	[36]
21	5-(3-hydroxy-4-methoxy-5-methylphenyl)-3-methylfuran-2-carboxylic acid	furan-2-carboxylic acid	Moderate anti-MRSA activities, Moderate antioxidant activity	[36]
22	5-(4-hydroxy-5-methoxy-2-methylphenyl)-3-methylfuran-2-carboxylic acid	furan-2-carboxylic acid	Moderate anti-MRSA activities, Moderate antioxidant activity	[36]
23*	orientalflavone 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	(2 <i>R</i> ,3 <i>R</i>)-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*	(8 <i>R</i> ,9 <i>S</i> ,10 <i>R</i> ,13 <i>S</i> ,14 <i>S</i> ,15 <i>S</i>)-15-hydroxy-10,13-dimethyl-6-methylene-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[<i>a</i>]phenanthrene-3,17(10 <i>H</i> ,14 <i>H</i>)-dione 3,17(10 <i>H</i> ,14 <i>H</i>)-dione	sterol	Moderate anti-TMV activity, Moderate cytotoxicity	[39]
34	11 α -hydroxy-6-methylene-androsta-1,4-diene-3,17-dione	sterol	Moderate anti-TMV activity, Moderate cytotoxicity	[39]
35	17 β -hydroxy-6-methylene-androsta-1,4-dien-3-one	sterol	Moderate anti-TMV activity, Nonsignificant cytotoxicity	[39]
36	17 β -hydroxy-6-methylene-androsta-1,4-diene-3,16-dione	sterol	Moderate anti-TMV activity, Nonsignificant cytotoxicity	[39]

37*	2-(4-methoxyphenyl)-3,5-dimethylbenzofuran-7-ol	2-arylbenzofurans	Moderate anti-TMV activity, Moderate cytotoxicity	[40]
38*	2-(4-methoxyphenyl)-3,5-dimethylbenzofuran-6-ol	2-arylbenzofurans	Moderate anti-TMV activity, Moderate cytotoxicity	[40]
39*	22-dimethyl-2 <i>H</i> -furo[3,4- <i>g</i>]chromen-8(6 <i>H</i>)-one	isobenzofurans	Moderate anti-TMV activity, Moderate cytotoxicity	[41]
40*	5-methoxy-22-dimethyl-2 <i>H</i> -furo[3,4- <i>g</i>]chromen-8(6 <i>H</i>)-one	isobenzofurans	Moderate anti-TMV activity, Moderate cytotoxicity	[41]
41*	6-hydroxy-5-(3-methyl-2-oxobut-3-enyl)isobenzofuran-1(3 <i>H</i>)-one	isobenzofurans	Moderate anti-TMV activity, Moderate cytotoxicity	[41]
42	(-)-dehydrodiconiferyl alcohol	phenylpropanoids	Moderate anti-TMV activity, Moderate cytotoxicity	[41]
43	pisatin	phenylpropanoids	Potent anti-TMV activity, Moderate cytotoxicity	[41]
44	turbinataphenol A	phenylpropanoids	Potent anti-TMV activity, Moderate cytotoxicity	[41]
45	nicotifuran A	phenylpropanoids	Moderate cytotoxicity	[41]
46	nicotabaamino glucoside	aminoglucoside	Weak cytotoxicity	[42]

^a * means new compounds. ^b Potent means the data was better than the positive control.

Yunyan 85 (a variety of *N. tabacum*).^[40]

Compounds **39–41** were characterized as three new isobenzofurans, while compounds **42–45** were four known phenylpropanoids.^[41] 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.^[42] 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 μ M 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 ningnanmycin (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.^[33,41] Compounds **23** and **24** exhibited good anti-MRSA activity with MIC₉₀ value of (38 $\pm$ 4) and (33 $\pm$ 3) μ g/mL, respectively. However, the MIC₉₀ value of the levofloxacin (positive control) was larger than (56 $\pm$ 6) μ g/mL.^[37]

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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