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Review Article

Chemical Outbreak for Tobacco Mosaic Virus Control

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Abstract

Tobacco mosaic virus (TMV) represents a paradigm in virology, and its control may open the way to effective treatment against phytoviruses. However, the use of chemicals to eliminate the virus from infected plants is very difficult. In this state of the art survey we include trials on a) natural compounds derived from organisms, b) synthetic compounds and c) plant or microorganism extracts, from 2006 to 2015. Plants have been the main source of natural products for anti-TMV tests in the last ten years, and *Nicotiana tabacum* was the main focus of research, particularly between 2014–2015. Since 2012, there has been a great increase in publications (+45%) and identified compounds (+241%). Between 2012–2015, an average of 31 papers were published and 140 compounds were tested each year, compared to 9 papers and 26 compounds in 2006–2011. Unfortunately, there is little information on the action mechanisms of newly discovered or modified compounds. Cross references to the basic structure of compounds is provided in this review. This chemical outbreak this massive interest in chemical solutions to TMV could be due to the increasing availability of instruments for the analysis of organic compounds. Alternatively Another explanation could be that the chemistry advances in synthesis, which have provided countless drugs with potential benefits for TMV control, have overwhelmed overloaded the plant pathology screening needed to discriminate between compounds and to provide useful agrochemicals for farmers.

Keywords: TMV; Chemotherapy; Thermotherapy; Natural product; Synthetic compound
Abbreviations: IMPDH (inosine monophosphate dehydrogenase); GHS (glutathione); NNM (ningnanmycin); NNI (non-nucleoside inhibitor); RT (reverse transcriptase); SAR (systemic acquired resistance), TMV (*Tobacco mosaic virus*)

Introduction

Besides the practical benefits related to controlling the *Tobacco mosaic virus* (TMV) and treating infected commercial hosts, TMV represents a paradigm in virology and represents a very difficult challenge for researcher. The virus is characterized by a high stability, thus conventional techniques of eradication from the soil have been tested over the last century. However, affordable control methods have not yet been obtained. The use of steam in the temperature range of 82–88°C has been shown to inactivate the virus in sap obtained from tomato leaves provided that the medium has been treated for a sufficient time (5–20 min). Similarly, the virus could be eliminated from roots, however higher temperatures are needed (90–95°C) together with extensive treatment times (10–20 min) (Broadbent *et al*., 1965). These findings highlighted how difficult it is to control the virus outside the laboratory or controlled conditions. The application of potassium hydroxide or calcium oxide to steam treatments in order to activate an exothermic reaction or the use of highly effective infrared film for soil solarization, provided unsatisfying results (Luvisi *et al*., 2015). The use of chemicals to eliminate the virus from infected plants also proved very difficult. Various inosine monophosphate dehydrogenase (IMPDH) inhibitors have been shown to heal infected plants (Guta *et al*., 2010; Panattoni *et al*., 2013a; Skiada *et al*., 2013; Panattoni *et al*., 2014; Guazzelli *et al*., 2015) and well-affirmed antiviral agents such as ribavirin appear to modulate virus infection via guanosine depletion (Panattoni *et al*., 2015). However the use of antiviral agents led to a limited efficacy in TMV control, probably because the antiviral drug mechanism can significantly interfere with many virus properties, thus affecting virus longevity (Luvisi *et al*., 2012). Moreover, although the permeation of many IMPDH chemicals through plant cells was easily achievable (Rinaldelli *et al*., 2012, 2014), the preparation of a formulated product was impracticable, due to high costs and legal disposal limits.

The search for TMV treatments has not stopped although no virus-curative agrochemicals are available in the market, except for the antiviral agent ningnanmycin (NNM), which seems to lead to curative rates of 30–60% (Ouyang *et al*., 2008). Unfortunately these results mainly refer to lab tests (*in vitro* or *in vivo* tests via the half leaf method) and more data on open-field applications are needded, thus the search for new compounds continues.

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Literature Review of Compounds from 2006–2015

Papers included in our literature survey were retrieved from the database of the Science Citation Index (SCI) (ISI, Web of Science, Philadelphia, USA), Science Direct (SD) (Elsevier, Amsterdam, Holland). We include trials published from 2006 to 2015 related to a) defined natural compounds derived from organisms, b) synthetic compounds, and c) plant extracts. We limited the analysis to papers in which the previously described compounds were applied *in vitro* or *in vivo* tests aimed at inhibiting TMV or protecting or curing plants from TMV infection. Trials evaluating systemic acquired resistance in which previously tested compounds were applied were not included.

Plants represent the main source of natural products for the anti-TMV tests carried out in the last ten years (Table 1). *Nicotiana* spp. was the species most investigated and *Nicotiana tabacum* was the main focus of research, particularly between 2014–2015. Much research also involved *Cassia* spp. *Aspergillus* spp. was the most investigated microorganism as the source of anti-TMV products.

From 2006–2011, about nine papers per year relating to anti-TMV tests were published (Fig. 1). These works mainly regarded synthetic compounds. Since 2012, there has been a rapid increase in publications (+45%) and compounds showing anti-TMV activity (+241%). While in 2013 a slight increase was observed in papers (+6%), this trend was repeated in 2014 (+106 and +121% in papers and compounds, respectively) and 2015 (+57 and + 9% in papers and compounds, respectively). In the last two years, an increase in research in natural rather than synthetic products was observed both in terms of the number of papers published and in the compounds identified (Fig. 1).

On average, from 2012–2015, 31 papers per year were published, while nine papers per year were published from 2006–2011. Similarly, in 2012–2015, 140 compounds were tested, compared to 26 compounds per year evaluated from 2006–2011.

Of the studies on natural products, the number of publications increased dramatically in 2014 and 2015 (+186% and +145%, respectively) (Fig. 2). In the last two years, more than 200 compounds showing anti-TMV activity were discovered, compared to about 80 compounds identified in the previous eight years. In 2012 there was a massive increase in publications on synthetic compounds (+157%) (Fig. 2) but findings have fluctuated, due to a small decrease in 2013 (-15%) followed by an increase in 2014 (+100%). A further decrease was observed in 2015 (-58%).

Most papers published in the last ten years belong to chemistry-oriented journals. Thus, while extraction and purification methods or synthesis and determination protocols have been thoroughly reported on, little or no information has been provided on newly discovered or modified compounds. Thus, a cross reference to action mechanisms of basic structures was needed. In the following section we report the putative action mechanisms of the main groups of compounds recovered from a literature survey from 2006–2015.

Action Mechanism of Natural Products

Flavonoids reduce the TMV concentration in systemically infected tobacco plants. As reported by Krcatović *et al.* (2008), the reduction seems limited to an early stage of infection and is associated with an induced production of salicylic acid and kaempferol, without direct virus inactivation, since flavonoids were not found to bind to TMV particles. Thus, their effect may be mainly associated with a defensive role.

Regarding chromone alkaloids, the activity against HIV is assumed to be associated with irreversible binding to glycoprotein GP120 (Houghton *et al*., 1994). In addition, the inhibitory effect caused by hydrophobic interaction of chromones was observed in the active site of HIV-1 protease. This interaction was deemed to be important because the enzyme was frequently used in programs for developing novel molecules, which are effective against the human virus (Ungwitayatorn *et al*., 2011). Conversely, no information was available for the plant host.

Terpenes may slightly increase cellular glutathione (GHS) levels in tobacco and have been found to lead to lipid peroxidation (Gullner *et al.*, 1999). Further effects are related to the induction of glutathione S-transferase and to a lesser extent, also to the increased efficacy of other enzymes such as glutathione reductase or ascorbate peroxidase. Thus, increased levels of GSH and the activities of GSH-related enzymes, reduce the necrotization of virus-infected tissues. Sesqui- and diterpenoids have also been identified as compounds involved in systemic acquired resistance (SAR) in TMV infected plant parts (Choi *et al*., 2006).

With regards to coumarins, the reduction of scopolin and scopoletin has been associated with plants that are less resistant to viral aggression (Chong *et al*., 2002). When TMV led to the development of necrotic lesions on leaves, the concentration of scopoletin increased in the nearer tissues. Glucosylation seems to be required for the production of this chemical which seems to directly attack the virus. The involvement of scopoletin in reactive oxygen responses has also been suggested. The glucosylated form scopolin accumulates in vast amounts in tobacco during the hypersensitive response to TMV. Overexpressing plants have been found to show necrosis from the early stage of infection, while the development of lesions was rapid. The content of virus in necrotic lesions is similar in transgenic and in wild-type plants (Gachon *et al*., 2004).

Action Mechanism of Synthetic Products

In HIV replication, the reverse transcriptase (RT) can be

Table 1: Number of papers (published in 2006-2015) in which natural product sources (plants, fungi, chromista, bacteria, animals) were used to extract compounds for anti-TMV tests

Natural product source	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Plants											
Nicotiana spp.		1	1				1		9	16	28
Cassia spp.							1	3	5	4	13
Garcinia spp.								1	1	2	4
Munronia spp.							2			2	4
Arundina graminifolia								1		2	3
Brucea javanica			1		1			1			3
Lindera caudata									1	2	3
Comastoma spp.										2	2
Ilex oblonga		2									2
Schisandra spp.										2	2
Swertia spp.							1			1	2
Artemisia princeps										1	1
Azadirachta indica			1								1
Coreopsis drummondii				1							1
Hypericum chinense										1	1
Melia toosendan									1		1
Picrasma quassioides				1							1
Rhus javanica		1									1
Satureja montana					1						1
Teucrium arduini						1					1
Ziziphus jujuba								1			1
Fungi											
Aspergillus spp.			1	1					2	3	7
Penicillium oxalicum										2	2
Others											
Chromista, Bacteria [..]	1	1				1	1				4

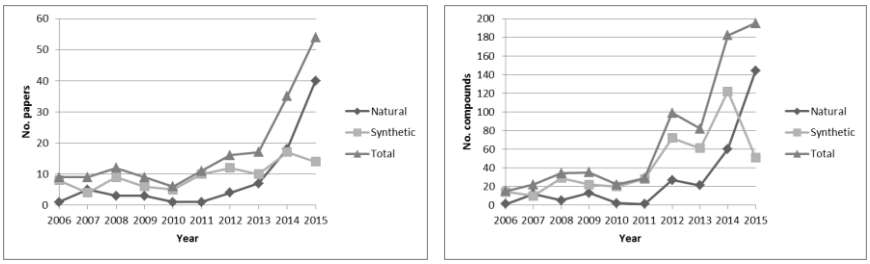

Fig. 1: Number of papers reporting anti-TMV tests with natural or synthetic compounds or a number of corresponding compounds, published during 2006-2015

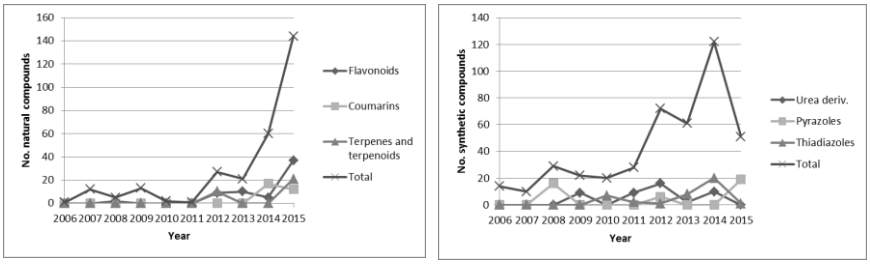

Fig. 2: Number of natural or synthetic compounds grouped by chemical structures, published from 2006-2015

inhibited by thiourea derivatives. Thus, these compounds can be considered as RT-related non-nucleoside inhibitors (NNIs) (Vig *et al*., 1998). Compounds derived from binding phenethyl-thiazolyl-thiourea can strongly interact with HIV-1 RT (D'Cruz and Uckun, 2006). In plants, virus-urea interaction has been investigated in TMV dissociation and subunit denaturation. Bonafe *et al*. (1998) showed how the apparent free energy associated with denaturation by urea for TMV protein coat was very low, almost null. The apparent urea stoichiometry of dissociation and denaturation of further viral agents has been calculated (Santos *et al*., 2008).

Quinazolines and quinazolinones are interesting classes of fused heterocycles, characterized by a broad range

of biological properties (Connolly *et al*., 2005). The antiviral action mechanism has been investigated in animal cells, where the slow-down of protein kinase seems to represent the key-factor (Schleiss *et al*., 2008).

Benzothiadiazole effectiveness in SAR enhancing has been investigated in tobacco infected by TMV (Friedrich *et al*., 1996). In hosts genetically modified to express the nahG gene, this compound seems to increase its expression, leading to increased tolerance to infection. Benzothidiazole also seems to be related to an increase in salicylic acid concentration, due to the induction of the SAR signal transduction pathway. However, the compound seems to lead to a protective effect also in non-genetically modified hosts (Kusajima *et al*., 2010).

Pathogen related (PR) genes such as PR-1, which is related to the salicylic acid-mediated signal transduction pathway, is positively regulated by pyrazole derivative (Ouyang *et al*., 2008). Treatment was shown to increase the activity of peroxidase and superoxide dismutase. Tests of fluorescence quenching and red-shift indicates how pyrazole derivatives showed an affinity with two coat proteins (CP) (4S and 20S) of the virus, while no affinity was reported for TMV RNA. As suggested by the authors, TMV CP defends viral RNA from degradation leading to ribonuclease, supporting the production of normal virus particlex. Thus the antiviral activity of chemicals has also been suggested as having an affinity towards TMV CP.

A New Benchmark: Ningnanmycin

Ningnanmycin (NNM) is becoming a benchmark for evaluating the potential anti-TMV activity of chemicals (derived from natural or synthetic products). Comparisons using NNM are commonly accepted by researchers as being a 'reference agrochemical'. However this product is unusual in European or American research, where it appears that no scientific tests have been carried out. Moreover, it is rarely found in catalogues of non-Asian dealers, suggesting a very uncommon use by farmers outside Asia. NNM is produced in China and it is commonly registered as a fungicide.

NNM can be obtained from the fermentation broth of *Strepcomyces noursei* var *xichangensisn* which is classified as a cytosine nucleoside type antibiotic. The compound is not considered as a pollutant and is characterized by a broad spectrum of actions although it is mainly applied against TMV.

Further studies suggest that NNM can turn on various pathways linked to disease protection, inducing systemic resistance to the virus in tobacco plants (Han *et al*., 2014). NNM is able to increase the levels of the Rubisco enzyme, alleviating photosynthesis damage by reducing TMV CP inside chloroplasts. This feature is linked to the negative interaction of CP with PS II, which is reduced in diseased hosts. NNM also reduces the quantity of CP, due to the inhibition of polymerization of TMV CP (Han *et al*., 2014) and increases tolerance in infected plants thanks to CP degradation (Xiang *et al*., 1995).

NNM seems to increase β-1,3-glucanases (Han *et al*., 2014). These enzymes have been linked to resistance-related processes related to virus aggression, because their production was promoted by viral infection (Kauffmann *et al*., 1987; Gorovits *et al*., 2007). The compound also promotes the activity of phenylalanine ammonia lyase, peroxidase and superoxide dismutase, increasing plant resistance against TMV (Fan *et al*., 2011).

In addition, a diffuse increase in pathogenesis-related molecules commonly related to SAR mechanisms, has been observed in plants treated with NNM, which induced more pathogenesis-related proteins that are known to be induced by the application of salicylic acid (Han *et al*., 2014). Finally, NNM treatment up-regulated the expression of non-expressor PR-1, the key player in activating the jasmonate signaling pathway.

Changes in Evaluation Methods

With regard to virus elimination in plants using laboratory-related techniques (i.e., tissue culture, embryogenesis, thermotherapy, chemotherapy), the success – or more commonly the lack of success – using the TMV technique was estimated by assessing the production of virus-free plants, organs or cultures (Panattoni *et al.*, 2013b). Merely attempting to produce virus-free plants is not sufficient to identify treatment factors (i.e., time of treatments or concentration of chemicals) as the virus biology or structure can significantly interfere with the final target: successful treatments and virus elimination. Thus, although some antiviral techniques seem to slow-down or even stop the viral replication (Luvisi *et al*., 2012), TMV eradication seems difficult.

On the other hand, the half-leaf method has been commonly used to assay the inactivation activity of chemicals in NNM comparisons (Chen *et al*., 2009; Yan *et al*., 2010). Almost all the literature on TMV control included in this review reports on how the half-leaf method can be applied. Generally, fresh leaves from TMV-infected tobacco plants were cut in halves along the main vein, immersing the halves into solutions of different concentrations for 20 min. The halves were then cultured at 25°C for 72 h, counting local lesions (Chen, 1990; Wang *et al*., 2010). More detailed tests are reported by Wang *et al*. (2010), who defined one of the most cited approaches for in vivo anti-TMV chemical evaluation, assessing protective, inactivation or curative effects of the chemicals. The protective effect was estimated by smearing the compound solution on half leaves on *N. tabacum*, followed by TMV mechanical inoculation of the whole leaf 12 h after treatment. Local lesions were counted after 3–4 days. The inactivation effect was assessed by mixing the compound solution with purified TMV for 30 min. Half leaf inoculation was carried out with a mixed solution or purified TMV, assessing local lesion after 3–4 days. The curative

effect was assessed after inoculation of the whole leaves and treatment of half leaves with the compounds. No info on the time between inoculation and treatment was provided but a description led to a sequential treatment step after inoculation. Local lesions were assessed after 3–4 days (Wang *et al*., 2010).

Wang *et al*. (2010) assays seem more orientated to the screening of potential antiviral activities of compounds than evaluating the drug for plant healing or virus elimination. Irrespectively of the parameters assessed, the local lesion count did not lead to a 100% reduction in tested drugs (few lesions were counted in treated plants). Similarly, at least a mild effect of the compounds (about a 10–20% reduction) was almost always reported. Thus, considering the tens of compounds discovered/synthetized in the last ten years, most lie in a "grey zone" of effectiveness which should be further investigated in order to validate their antiviral effectiveness.

The Outbreak

With regard to the most recent literature, in just twelve months (April 2015 – May 2016) many compounds were found (natural products derived mainly from plants) or synthesized. Here we report a list of the main groups of compound available for TMV control.

Natural Products

Screening anti-TMV substances from fungi has become a hot research topic and *Pleurotaceae*, *Tricholomataceae* and *Russulaceae* play a key role (He *et al*., 2016).

Flavonoids: Flavones (18 molecules) were successfully isolated from *Cassia siamea*, *Garcinia bracteata*, *Hypericum chinense* or *N. tabacum*. Of these, eight compounds were unknown. At least three flavones showed an inhibition rate of TMV similar to NNM.

Chemical investigation of stems of *C. siamea* led to the isolation of five known compounds and two novel ones (siameflavones A and B). The flavones were characterized by low antiviral properties, causing a TMV inhibition of 12–19% (Zhou *et al.*, 2015a).

A single new flavone was isolated from stems of *G. bracteata*. The compound, 7-methoxy-4',6-dihydroxy'-8-isobutyryl-flavone, showed significant anti-TMV properties, leading to a 28% viral inhibition (Li *et al*., 2015a).

Analysis of various organs and tissues of *H. chinense* identified two new flavones, 6,4′-dimethoxy-8-formylflavone and 6,7-dimethoxy-8-acetyl-4′-hydroxyflavone, as well as a further five flavones previously identified, of which the inhibitory effect against TMV was up to 31% (Zhou *et al*., 2015b).

Three new isoflavones, 4′,8-dihydroxy-6,7-dimethoxyisoflavone, 4′,6-dihydroxy-8-methoxycarbonyl-7-methoxyisoflavone and 4′,7-dimethoxy-8-hydroxymethyl-6-hydroxyisoflavone were successfully isolated from *N. tabacum*, leading to inhibition rates of 25%, 23% and 27%, respectively (Li *et al*., 2015b).

Coumarins: Coumarins (five molecules) were isolated from plants (*Lindera caudate*, *N. tabacum*). Additional coumarines (nine molecules) were isolated from fungi (*Penicillium oxalicum*). Generally, the inhibition rate was low compared to NNM.

L. caudate led to the discovery of a new isocoumarin, caudacoumarin D, which was isolated from its bark and showed an inhibition rate of 17% (Wang *et al*., 2015).

The novel compounds, tabaisocoumarins D and E, together with two chemicals previously characterized, were identified from the leaves of *N. tabacum*, leading to an 11–18% inhibition against TMV (Wang *et al*., 2016).

Novel isocumarins were isolated from chemicals produced by the fermentation of *P. oxalicum* 0403 (terrecoumarins A-C), together with a further six isocoumarins previously characterized. Generally, the effects of the compounds on TMV were mild, with an 11-19% inhibition, however for one compound the rate was even 25% (Li *et al*., 2015c).

Terpenes and terpenoids: Terpenes, terpenoids and terpene derivatives were isolated from plants (*N. tabacum*, *Munronia henryi* and *Spiraea japonica*). Of the 38 different compounds, 17 were unknown. A higher inhibition rate than NNM was frequently observed.

Leaves of *N. tabacum* represent good sources of sesquiterpenes. Nicosesquiterpene A and B are novel sesquiterpenes, which showed inhibition rates of 36.7% and 45.6%, respectively (Shen *et al*., 2016). Other novel sesquiterpenes such as nicotianasesterpenes A and B (Shen *et al*., 2015a) or tabasesquiterpenes A-C (Shang *et al*., 2016) were more efficient than NNM, showing inhibition rates in the range of 34-35%. Another eight sesquiterpenes led to inhibition rates in the range of 18-29% (Shen *et al*., 2015a; Shang *et al*., 2016).

High inhibition rates (69-93%) were also observed from six terpenes derived from the ethanolic extracts of the whole plant of *S. japonica* (Ma *et al*., 2016). The spiramidine C2, a novel compound, was found to be effective in TMV control, as well as four other novel chemicals, (two atisine-type diterpene alkaloids and two atisane-type diterpenes) and other previously identified compounds.

In ethanolic extracts obtained from *M. henryi*, in addition to previously characterized limonoids, other novel limonoids, a diterpenoid and a phytosterol, were identified and a strong antiviral activity was also observed (Yan *et al*., 2015).

Chromones: Chromones (three novel compounds) were isolated from plants (*C. fistula* and *N. tabacum*).

The 6-acetyl-7-methoxy-2,3-dimethyl-4H-chromen-4-one was isolated from the steam of *N. tabacum* , which showed potential anti-TMV activity with inhibition rates of 25% (Zhang *et al*., 2015a). Two bischromones with unique coupling patterns (fistulains A and B) were isolated in tissues collected from *C. fistula* plants, showing a promising

efficacy (Zhou *et al*., 2015c).

Phenyl-derivatives: Phenyl derivate and phenylpropanoids (11 compounds) were isolated from plants (*Arundina graminifolia*, *G. multiflora* and *N. tabacum*) and fungi (*Aspergillus terreus*). Of these eight compounds were unknown. Three exhibited similar anti-TMV activities to NNM.

In stems of *N. tabacum* three new phenylpropanoids were found, 3-(6-methoxy-3-oxo-1, 3-dihydroisobenzofuran-5-yl)-3-oxopropyl acetate, 3-hydroxy-1-(6-methoxy-1, 3-dihydroisobenzofuran-5-yl) propan-1-one, and 3-hydroxy-1-(6- methyl-1, 3-dihydroisobenzofuran-5-yl) propan-1-one, together with three known phenylpropanoids (Kong *et al*., 2015). Inhibition rates were between 17% and 29% for most molecules, but two led to a strong inhibition in virus activity (35%). A new biphenyl (tababiphenyl F) was isolated in leaves, with an inhibition rate of 23% (Liu *et al*., 2015).

Another phenylpropanoid, 6-(3-hydroxypropanoyl)-5-hydroxymethyl-isobenzofuran-1(3H)-one, was isolated from the whole plant of *A. graminifolia*, exhibiting an inhibition effect of 23% against the virus (Dong *et al*., 2015).

Two new biphenyls (multiflorabiphenyls A and B) extracted from *G. multiflora* led to a 25% and 28% virus inhibition (Xu *et al*., 2016).

Terrephenol C, phenyl derivated butyrolactone, was identified among chemicals produced by the fermentation of *A. terreus*. The effects of this chemical on the virus were mild, with a 17% inhibition (Zhou *et al*., 2015d).

Phenol-derivatives: Phenol-derivatives (eight compounds) were isolated from plants (*A. gramnifolia*, *Givotia rottleriformis* and *Swertia elata*). Four compounds were unknown but anti-TMV activity was weak compared to NNM.

The 2-(benzoyloxy) benzoic acid, which was shown to reduce leaf necrosis and TMV-coat protein levels in systemic leaves (Kamatham *et al*., 2016) was identified from seed tissues of *G. rottleriformis*.

A new phenolic compound, gramniphenol I, was isolated from the whole plant of *A. gramnifolia*, exhibiting a notable antiviral effect (17% of inhibitor activity) (Li *et al*., 2015d).

Two novel xanthones were identified from whole herb of *S. elata*, as well as a previously characterized xanthone, with a 15–29% of inhibition (Jiang *et al*., 2015).

Furan-derivatives: Furan-derivatives (eight compounds) were isolated from plants (*N. tabacum*). Four compounds were unknown and anti-TMV activity was similar to NNM in two cases.

A new dihydrobenzofuran neolignan, tobdihydrofuran A, was isolated from the stems of *N. tabacum*, showing an inhibition rate of 29% (Zhang *et al*., 2015b).

Lactones: Lactones (seven compounds) were isolated from plants (*N. tabacum*) or fungi (*Aspergillus versicolor*). Four novel compounds were identified, showing a good anti-TMV activity.

Two new benzolactones, 5-methyl-6-prenyl-isobenzofuran-1(3H)-one, 5-hydroxymethyl-6-prenyl-isobenzofuran-1(3H)-one were isolated in leaves of *N. tabacum*, as well as other previously identified phenolic chemicals (Shen *et al*., 2015b). Tests indicated that lactones led to significant antiviral activity (17–26% of inhibition).

Asperphenol C, a new butyrolactone, was identified among chemicals produced by the fermentation of *A. versicolor*. The effects of this chemical on the virus were significant, with a 22% inhibition rate (Li *et al*., 2015e).

Alkaloids: Alkaloids were isolated from plants (*C. siamea* and *C. fistula*). Of the 12 different compounds, five were unknown. Inhibition rates varied from high to weak compared to NNM. Three new tricyclic alkaloids, siamalkaloids A-C, together with three known alkaloids were isolated from the twigs of *C. siamea* (Wu *et al*., 2016a). Simalkaloid C exhibited an inhibition rate of up to 35%.

Fistulatins (A and B) are novel isoquinoline alkaloids identified in tissues of *C. fistula*, as well as other previously characterized alkaloids. Findings indicated a mild effect on the virus (15-24% inhibition) (Wu *et al*., 2016b).

Aromatic compound derivatives: Two new isoindolin-1-ones, 2-(2-hydroxyethyl)-5-methyl-6-(3- methylbut-2-enyl) isoindolin-1-one and 2,5-dimethyl-6-(3-methylbut-2-enyl)-isoindolin-1-one, were identified from tissues of tobacco plants. Tests indicated a significant antiviral effect (48% and 46% of inhibition, respectively) (Kong *et al*., 2016).

Glycoprotein: GP-1, from *Streptomyces kanasensis* ZX01, is a new antiviral glycoprotein that is capable of breaking the TMV structure, thus inhibiting the infection process and reducing the virus in cells (Zhang *et al*., 2016). GP-1 also promote systematic resistance in host cells, according to the findings on the increase in protection enzymes, reduction in malondialdehyde and up-regulation of PR genes.

Synthetic Products

Thiadiazole: Tests on synthetic 2-substituted methlthio-5-(4-amino-2-methylpyrimidin-5-yl-)-1,3,4-thiadiazole derivatives showed a comparable antiviral activity of the novel compound to NNM (Wu *et al*., 2016c).

Quinazoline: Novel 1,4-pentadien-3-one derivatives containing 4-thioquinazoline moiety were designed and synthesized. Findings suggested that many of the proposed chemicals exhibited a good antiviral property for *in vivo* treatments against the virus (Long *et al*., 2015).

A series of novel 4-thioquinazoline derivatives containing chalcone moiety were planned and produced (Wan *et al*., 2015). Compounds M2 and M6 were characterized by interesting protection properties *in vivo*, better than those observed with ribavirin.

Aromatic compound derivatives: A group of phenanthrene-containing N-heterocyclic chemicals (33 compounds) were designed and synthesized. The molecules were planned on the basis of the intermolecular interaction

of antofine and viral RNA (Yu *et al*., 2016). Three of them showed a higher activity than the antofine and ribavirin from which they were derived.

The synthesis of a novel group of sulfonamide and carbamate derivatives of 7-azaindole and tests highlighted their antiviral properties (Sudhamani *et al*., 2016). The biological assay indicated that the chemicals 4-nitrophenyl 1H-pyrrolo [2,3-b] pyridine-1-carboxylate and 4-nitrobenzyl 1H-pyrrolo [2,3-b] pyridine-1-carboxylate showed a high inhibition against TMV.

New 2-substituted methylthio-5-(4-amino-2-methylpyrimidin-5-yl-)-1,3,4-oxadiazole derivatives were designed and produced (Wu *et al*., 2015a). Six compounds resembled the curative effect of NNM against the virus.

Alkaloids: To evaluate the antiviral properties of β-carboline alkaloids, four types of structurally new β-carboline alkaloid analogues, with indole-fused six to nine-membered ring motifs, were designed, synthesized, and tested for the inhibition of TMV (Yang *et al*., 2016). Bioassay tests showed that most of these chemicals had interesting anti-TMV activities.

Pyrazoles: In order to investigate the biological activity of novel pyrazole derivatives, a series of N-(substituted-1H-pyrazol-4-yl)-1H-pyrazole-3(5)-carboxamides with bi-heterocyclic scaffold were designed and synthesized from ethyl 5-alkyl-1H-pyrazole-3-carboxylate via several steps (Zhang *et al*., 2015c). The bioassay data showed that many of the synthesized chemicals led to strong inhibition of TMV, especially two compounds possessing a higher activity than NNM or ribavirin.

Hydrocarbon derivatives: A series of 1,5-diaryl-1,4-pentadien-3-one derivatives bearing an emodin group were produced using natural products as base-compounds (Wu *et al*., 2015b). One compound showed an appreciable curative bioactivity on TMV, which was superior to NNM.

New triarylmethane derivatives were produced following a one-pot, two-component method via Friedel-Crafts alkylation of electron-rich arenes with various aldehydes, exhibiting high antiviral activities against TMV (Revaprasadu *et al*., 2016).

Amines: In the cotton plant, gossypol was identified as a key component of the defense system against pathogens and insects. Gossypol alkylamine Schiff bases, oxime and hydrazone derivatives were synthesized in order to identify novel analogs of gossypol with enhanced plant defense activity (Li *et al*., 2016). The results of biological tests showed that most synthesized gossypol derivatives exhibited a higher anti-TMV activity than the original compound.

Conclusion

Chemistry is the most widely used approach to pest management, thanks to the high efficiency of compounds against many pests and the user-friendly applications. The increasing use of instruments to analyse organic compounds has led to the discovery of many molecules involved in SAR mechanisms and many compounds have been extracted in order to test against viruses. Similarly, chemistry advances in the synthesis of novel compounds can provide countless drugs with potential benefits in TMV or other virus controls. This has put high pressure on plant pathology screening needed to discriminate among compounds. There is a risk that thousands of "good TMV inhibitors" will be obtained thanks to incessant chemistry research but without properly assessing whether there are any really effective ones that might be useful for farmers. Some of the difficulties in identifying efficient compounds may well be due to the evaluation methods, because many natural compounds show some effect against TMV *in vitro* conditions or using the half leaf method. In addition minor small modifications to effective chemicals have led to the production of other very similar chemicals rather than anything truly novel. Thus a chemical approach will not be effective if it is not followed by further investigation, also against others viruses. Although not farm-oriented, tests on the recovery of infected plantlets after treatment are useful to recover local varieties or establish healthy mother plants, as reported in many thermotherapy or chemotherapy trials. The protective action of compounds should also be tested by simulating field conditions, for example using infected vectors. Thus, this chemical outbreak needs to be supported by "traditional" plant pathology tests in order to provide effective anti-viral compounds.

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