J Nat Med (2015) 69:451–462
DOI 10.1007/s11418-015-0910-z

MINI-REVIEW

Chikungunya virus (CHIKV) inhibitors from natural sources: a medicinal chemistry perspective

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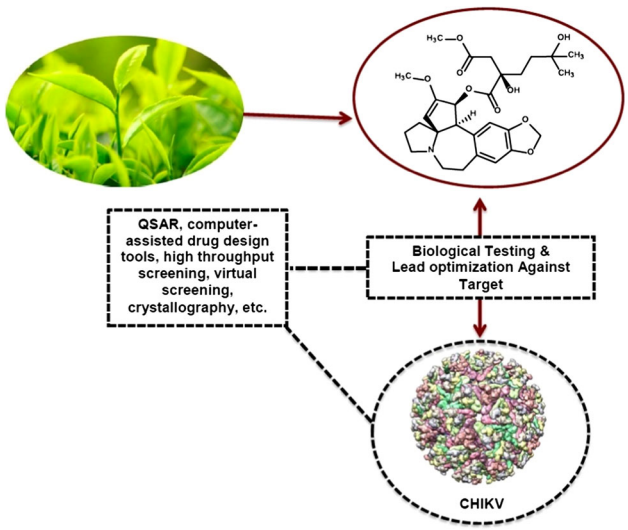
Received: 25 November 2014 / Accepted: 3 April 2015 / Published online: 29 April 2015

Abstract Chikungunya virus (CHIKV) is one of the re-emerging "neglected" tropical diseases whose recent outbreak affected not only Africa and South-East Asia but also several parts of America and Europe. To date, despite its serious nature, no antivirals or vaccines were developed in order to counter this resurgent infectious disease. The recent advancement in crystallography and availability of crystal structures of certain domains of CHIKV initiates the development of anti-CHIKV agents using structure-based drug design or synthetic medicinal chemistry approach. Despite the fact that almost 50 % of the new chemical entities against several biological targets were either obtained from natural products or natural product analogues, a very humble effort was directed towards identification of novel CHIKV inhibitors from natural products. In this review, besides a brief overview on CHIKV as well as the nature as a source of medicines, we highlight the current progress and future steps towards the discovery of CHIKV inhibitors from natural products. This report could pave the road towards the design of novel semi-synthetic derivatives with enhanced anti-viral activities.

Graphical Abstract



Keywords Chikungunya virus · Antivirals · Natural product

Introduction

Chikungunya virus (CHIKV) is a re-emerging arbovirus which belongs to the genus alphavirus and is responsible for chikungunya fever (CHIKF), severe joint pains and rash. The outbreak of CHIKF was first described in 1952 after an outbreak along the border of east African states, Tanganyika and Mozambique. This mosquito born alphavirus is transmitted by mosquitoes of the Aedes genus i.e. *Aedes ageypti*, *Aedes furcifier* and *Aedes albopictus.*

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Recent research highlighted the occurrence of A226 V mutation in the envelope glycoprotein of CHIKV which increased the CHIKV fitness in *A. albopictus* as well as improved transmissibility of the virus through *A. albopictus* [1]. In the mid twentieth century CHIKV emerged as a major epidemic in India and South East Asia [1, 2]. After several minor outbreaks in Africa, during 1999–2000 there was a large outbreak of CHIKV in the Republic of the Congo and further outbreak was documented in Gabon through *A. albopictus.* The beginning of 20th century observed a huge outbreak of chikungunya in India and several islands of South-East Asia [1, 3]. Since 2005, India and countries in South-East Asia have reported over 1.9 million cases (Fig. 1b). In 2007, CHIKV transmission was reported for the first time in Europe [4].

Recently the outbreak of chikungunya Caribbean island was the first of its kind in the western hemisphere with 66 confirmed cases and suspected cases of around 181 [3]. By the beginning of the year 2014 an estimated 30,000 cases of CHIKV were confirmed in the Caribbean island which brings the most alarming situation about the re-emerging status of chikungunya [3]. Since then several cases of CHIKV were documented in several parts of USA with an alarming rate (Fig. 1a). This sudden re-emergence of CHIKV across different parts of developed countries such as USA led to a rising effort from academic research to identify novel inhibitors targeting this re-emerging neglected disease.

Nature as a source of medicines: a brief overview

Chemical constituents isolated from natural products emerged as a source of novel therapeutics since early stages of drug discovery. Statistically around 50 % of the new chemical entities either obtained from natural products or natural product analogues [5–9]. Several natural products and natural product analogues have been widely used in a variety of different therapeutic indications, for instance, a few examples are presented here (Fig. 2a, b).

Natural sources for medicines against tropical diseases

The first spark of success was the discovery of the natural compound artemisinin (Fig. 2c) to treat malaria, one of the serious tropical diseases [11]. This was followed by a slow but steady increase in natural product based inhibitors towards re-emerging neglected tropical diseases especially against malaria and dengue virus (DENV) [10] (Fig. 2d). The natural product based treatment of malaria revolves around discovery and development of novel analogs/derivatives of highly active natural products e.g. salinosporamide A, a marine actinomycetes with antimalarial property, febrifugine and artemisinin [12]. The development of natural product inspired medicinal chemistry approach led to development of halofuginone, as well as some highly active febrifugine analogues as well as development of novel artemisinin analogues [12]. Similarly, several novel scaffolds were identified against different serotypes of DENV by exploiting the pool of natural products. This exploration led to identification of several terpenoids, polycyclic quinones, phenolics, alkaloids, flavonoids and polysaccharides against different serotypes of DENV [10]. The success in identifying a diverse set of natural product based scaffolds against DENV inspired the progress of natural product based inhibitors in targeting other neglected tropical diseases such as CHIKV.

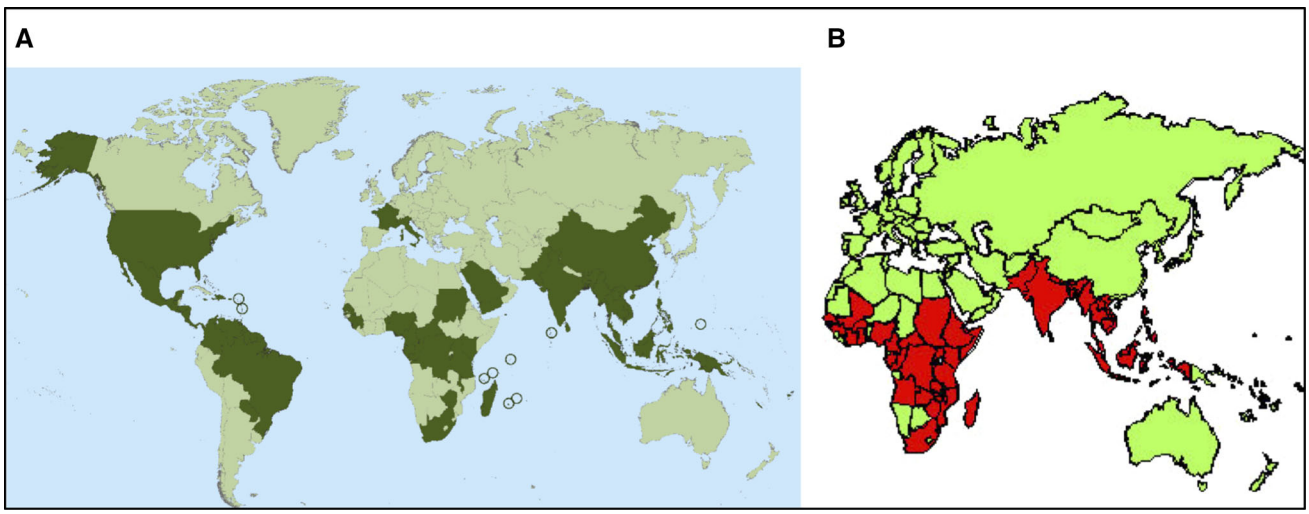

Fig. 1 **a** Countries and territories where chikungunya cases have been reported (highlighted in *green* as of November 18, 2014) and **b** cases of chikungunya outbreak during 1952–2006, the regions highlighted in '*red*' have been reported with chikungunya outbreak during that period [3]

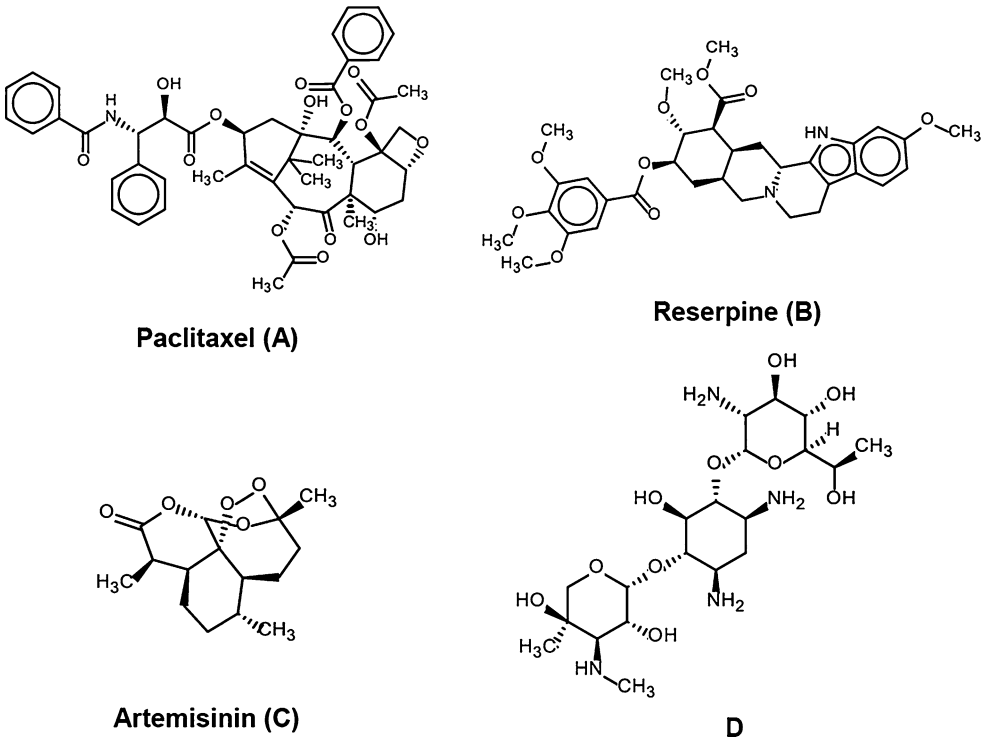

Fig. 2 Some example of natural products used in the treatment of several diseases. 2D structures of several natural product drugs used in the treatment of cancer (paclitaxel, **a**), hypertension (reserpine, **b**), malaria (artemisinin, **c**). Compound **d** [10] is one of the natural product which displayed inhibitory activity against neglected tropical disease, dengue virus infection

To best of our knowledge this review is first of its kind that highlights the current status in natural product based inhibitors targeting CHIKV.

Structural biology of CHIKV

The genome of CHIKV is a positive sense, single stranded RNA genome consists of two open reading frames, one in 5′ end which encodes non-structural proteases necessary for formation of viral replicase complexes and other 3′ end which encoded structural proteins, necessary for receptor binding and fusion with cell membrane [1, 4, 13].

Despite the advancement in crystallography and structural biology, the rational drug discovery targeting several domains of CHIKV genome were limited due to lack of crystallographic evidences. The crystal structures of CHIKV non-structural protease 2 (NSP2), non-structural protease 3 (NSP3) macrodomain and immature envelope glycoprotein complexes were resolved which emerged as a promising starting point to develop novel inhibitors targeting CHIKV [13].

Some of the recent reviews highlighted the detailed features of CHIKV genome and its application in modern era of antiviral drug discovery [1, 4, 13]. Herein, we emphasize on the structural features of CHIKV NSP2, NSP3 macrodomain and envelope glycoprotein complexes which emerged as crucial drug targets to develop novel antivirals targeting this re-emerging disease.

CHIKV NSP2 is responsible for protease and helicase activity and thus emerged as a crucial target to develop novel antivirals [1, 13]. Both N and C terminal domains are composed of α-helices and β-strands. The active site of CHIKV NSP2 is composed of residues located at C-terminal domains. The active site (Fig. 3a) of NSP2 consists of some key residues include Gln1039, Lys1045, Glu1157, His1222, Cys1239, Ser1293, Glu1296 and Met1297 (Fig. 3b) [1]. CHIKV NSP2 is a cysteine protease thus cysteine residues played an important role in enzyme activity. Structural analysis of NSP2 showed the existence of three N-terminal cysteine residues (Cys1013, Cys1057 and Cys1121) as well three C-terminal cysteine residues (Cys1233, Cys1274 and Cys1290). C-terminal cysteine residues Cys1233 and Cys1290 in combination with histidine residues (His1222, His1228, His1229 and His1236) could be associated with deprotonation mechanism and thus played a major role in viral pathogenesis [1].

Similar to NSP2, the crystal structure of N-terminal domain of CHIKV NSP3 emerged as a potential drug target to develop novel antivirals [15]. Advancement in crystallography led to discovery of high resolution crystal structure of CHIKV NSP3 in complex with ADP ribose (Fig. 4) [16]. NSP3 macrodomain believed to play a major role in metabolism of ADP ribose derivatives that played major role in cell regulatory function [1, 16]. Thus, understanding the binding region of ADP ribose derivative could serve as a starting point to develop novel inhibitors targeting CHIKV [1].

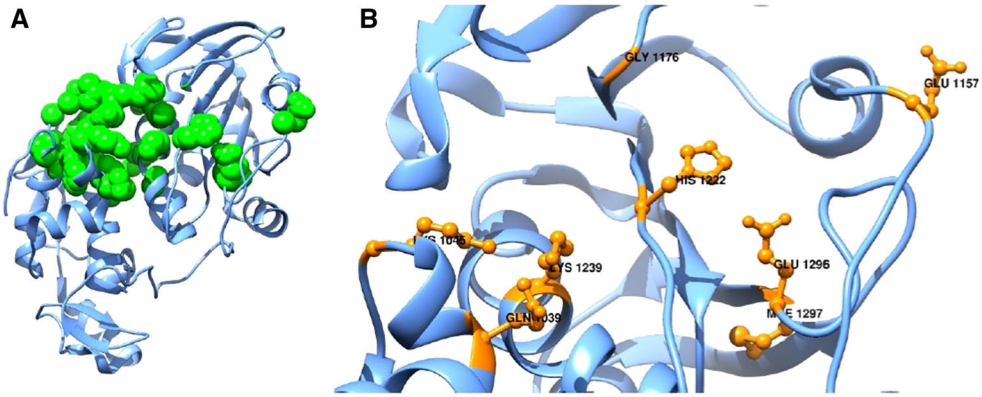

Fig. 3 Representation of CHIKV NSP2 (**PDB**: 3TRK [14]) which highlights the active site region of NSP2 (represented in *green spheres*, **a** as well as critical residues of active site are highlighted in *orange* (*ball* and *stick representation*, **b**)

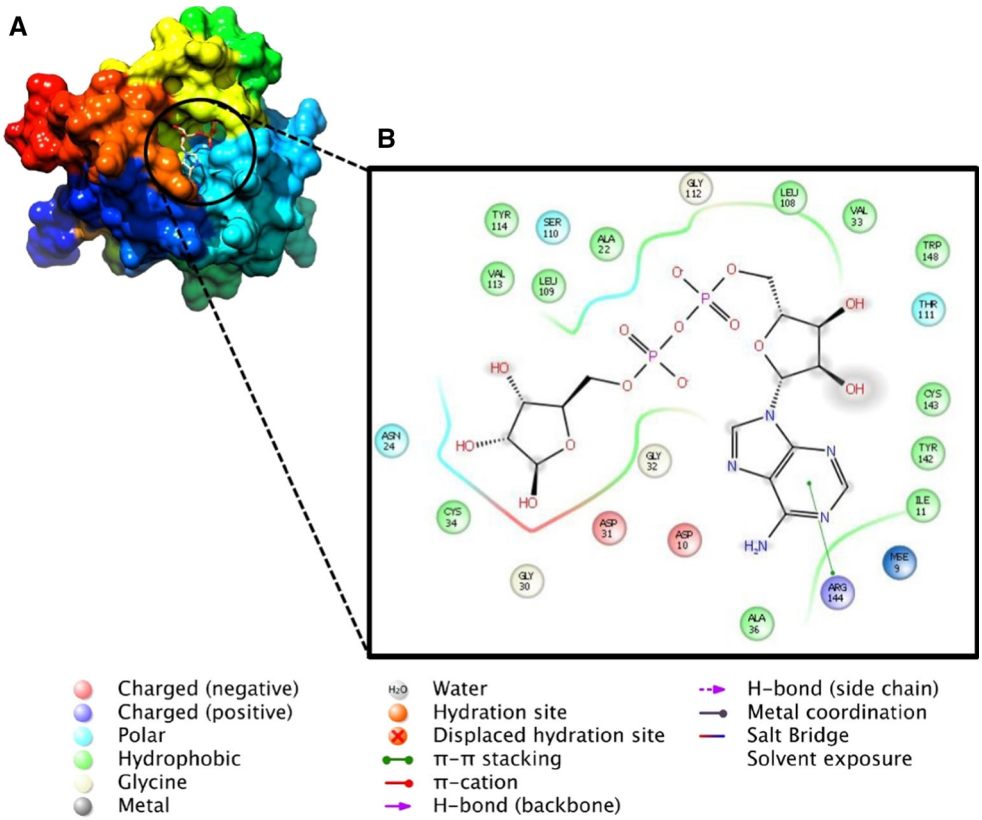

Fig. 4 Structure of CHIKV NSP3 macrodomain in complexed with ADP ribose derivative (**PDB**: 3GPO [16], **a**). The active site residues interacting with NSP3 active site might act as a foot print to design novel chemical entities targeting CHIKV NSP3

Similar to NSP3 macrodomain and NSP2, the mature envelope glycoprotein complex comprises of E1-E2-E3 structural proteins [17] (Fig. 5) led to identification of two plausible binding sites which might help in development of novel anti-CHIKV agents targeting viral structural proteins.

Till date, except the below-mentioned a few attempts (Sect. "Natural products targeting CHIKV: a medicinal chemistry perspective"), a humble effort has been directed rationally to design anti-CHIKV inhibitors targeting these drug targets. Therefore, further natural products and natural product-based optimization studies should be encouraged in order to identify novel chemical entities targeting different structural/non-structural proteins of the "neglected" CHIKV.

Natural products targeting CHIKV: a medicinal chemistry perspective

Despite the success of natural products as treatments for various diseases like cancer [18, 19], malaria [20], and HIV [21], the "neglected" CHIKV—and some others like Sindbis virus (SINV)—has not received much attention

from researchers. Herein, we compile the efforts that have been made so far towards the identification of novel leads from natural products that aimed to target CHIKV.

Recently the study of a Vietnamese plant species *Trigonostemon howii* led to isolation of a new tigliane-type diterpenoid, trigowiin A (**1**). Trigowiin A (**1**) (Fig. 6) exhibited moderate antiviral activity in a virus-cell-based assay against CHIKV. Antiviral testing of structurally related tigliane diterpenoids such as prostratin (**2**), phorbol (**3**), 12-O-tetradecanoylphorbol 13-acetate (TPA, **4**), and 4α-TPA (**5**) (Fig. 6) led to identification novel antiviral leads targeting CHIKV [22].

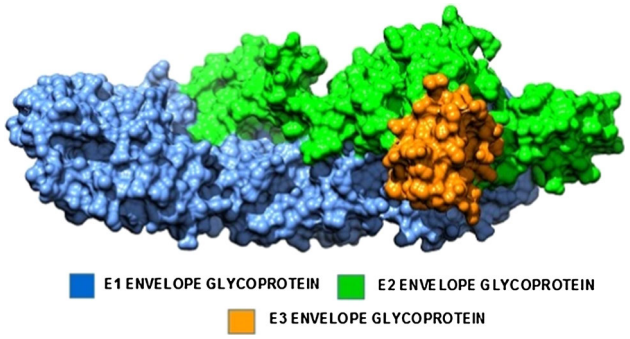

Fig. 5 The mature glycoprotein complex of CHIKV (**PDB**: 3N42 [17]) which might act as a promising target to develop novel drug molecules targeting CHIKV structural proteins

Besides the moderate CHIKV inhibitory activity possessed by trigowiin A, prostratin and TPA, two structurally related tigliane-type diterpenoids, displayed potent and selective anti-CHIKV activity (Table 1) [22]. The strong inhibitory activity observed by prostratin (EC_{50} = 2.6 μM and a selectivity index of 30) might initiate future efforts to design optimized novel tigliane type diterpenoids-based inhibitors since this chemical scaffold proved potential as CHIKV inhibitor (Table 1) [22]. Bourjit et al. [22.] postulated that activation of the signal transduction enzyme protein kinase C (PKC) could be the main reason behind the antiviral activity of these molecules (compounds 1–5) on CHIKV which is quite similar to the proposed mechanism of TPA on HIV replication [23]. Thus the structure and pharmacophoric features of these compounds might be effective in order to develop specific PKC activators as potential anti-CHIKV agents.

In an effort to identify novel scaffolds targeting CHIKV replication, an extensive study taking in account 820 ethyl

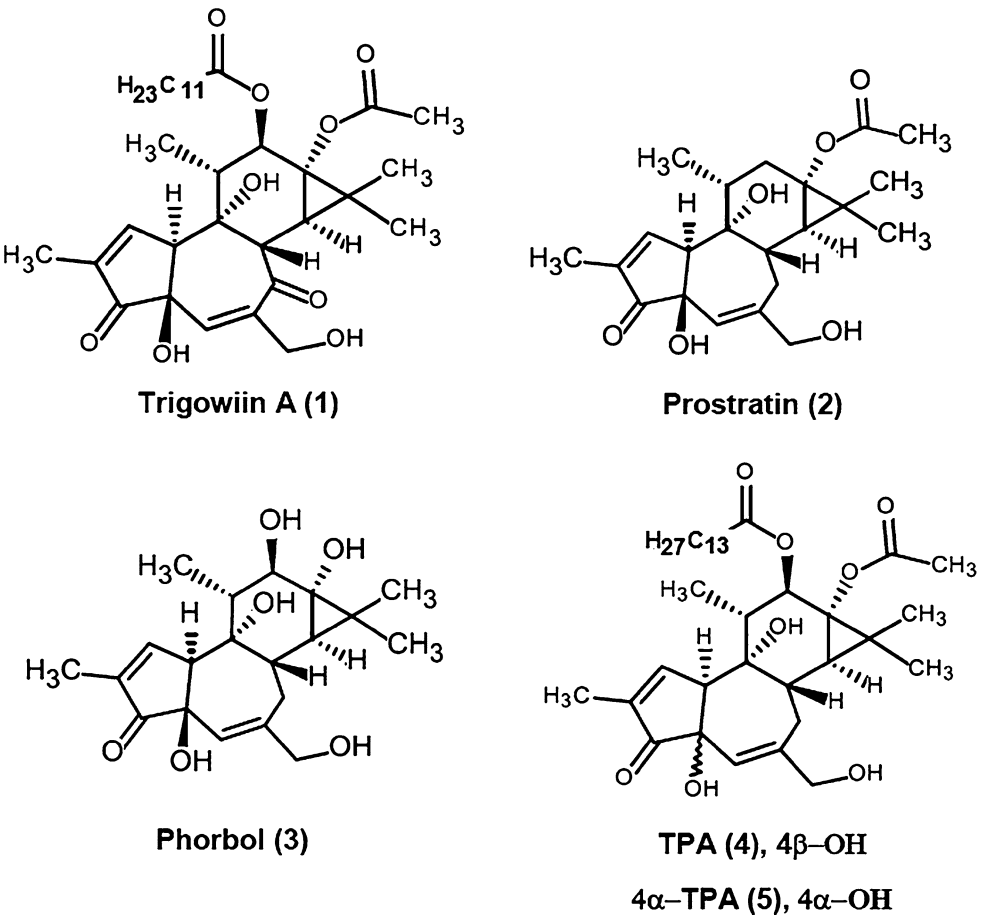

Fig. 6 2D structural representation of tigliane-type diterpenoids trigowiin A (**1**) prostratin (**2**), phorbol (**3**), 12-*O*-tetradecanoylphorbol 13-acetate (TPA, **4**), and 4α-TPA (**5**)

Table 1 Antiviral activities of compounds **1–5** in vero cells against CHIKV [22]

Compounds	CC_{50} vero cells (μM)	EC_{50} CHIKV (μM)
Compound **1**	>100	43.5 ± 12.8
Compound **2**	79.0 ± 17.4	2.6 ± 1.5
Compound **3**	>343	>343
Compound **4**	5.7 ± 1.7	0.0029 ± 0.0003
Compound **5**	5.3 ± 0.6	2.8 ± 0.5

acetate extracts of Madagascan plants was performed in a virus-cell-based assay for CHIKV. This exploration led to identification of one new(*E*)-tridec-2-en-4-ynedioic acid named anacolosine (**6**), together with three known acetylenic acids, the octadeca-9,11,13-triynoic acid (**7**), (13*E*)-octadec-13-en-9,11-diynoic acid (**8**), (13*E*)-octadec-13-en-11-ynoic acid (**9**), two terpenoids, lupenone (**10**) and β-amyrone (**11**), and one cyanogenic glycoside, (*S*)-sambunigrin (**12**) (Fig. 7) [24].

The inhibitory activity of these chemical entities was tested against CHIKV in a viral cell-based assay. Two terpenoids, lupenone (**10**) and β-amyrone (**11**) displayed moderate inhibitory activity against CHIKV with EC_{50} 77 μM and 86 μM, respectively (Table 2) [24]. The inhibitory effect of lupenone (**10**) further confirmed that lupane based triterpenoid skeleton are selective inhibitors of CHIKV and can be further optimized in order to provide semi-synthetic derivatives with enhanced anti-viral activity.

Further, bioassay guided purification and virus cell-based assay of an EtOAc extract of the leaves of *Croton mauritianus* led to isolation of two phorbol esters 12-*O*-decanoylphorbol-13-acetate and 12-*O*-decanoyl-7-hydroperoxy-phorbol-5-ene-13-acetate as well as five ionone derivatives i.e. loliolide, vomifoliol, dehydrovomifoliol, annuionone D and bluemol C [25]. Virus cell based assay identifies 12-*O*-decanoylphorbol-13-acetate (**13**) and 12-*O*-decanoyl-7-hydroperoxy-phorbol-5-ene-13-acetate (**14**) (Fig. 8) as novel inhibitors of CHIKV with EC_{50} of 2.4 ± 0.3 μM and 4.0 ± 0.8 μM, respectively [25]. Exploring the inhibitory effect of structural analogues of these phorbol esters and side chains associated with the main skeleton might act as an area of further exploration to target CHIKV.

Moreover, A study has been performed on the bark and the wood of a rare endemic plant *Trigonostemon cherrieri* led to isolation of highly oxygenated daphnane diterpenoid orthoesters (DDO) bearing an uncommon chlorinated moiety: trigocherrins A (**15**), B (**16**) and F (**17**) (Fig. 9) and trigocherriolides A (**18**), B (**19**) and C (**20**) (Fig. 9) displayed moderate to fair activity against CHIKV with EC_{50} ranging from 1.5 to 3.9 μM [26]. Trigocherrins B was identified as the most active diterpenoid with EC_{50} 1.5 μM against CHIKV in a virus cell based assay (Table 3) [26]. These DDOs further possessed significant inhibitory activity against several other neglected re-emerging pathogens including Sindbis virus (SINV), Semliki forest virus (SFV) and DENV and thus can be explored further to design novel leads targeting several re-emerging viruses.

In another study, the aqueous-ethanolic and ethanolic extracts of the leaves of *Vitex negundo*, *Hyptis suaveolens* and roots of *Decalepis hamiltonii* were studied for their antiviral activity against CHIKV. The extracts were found to be effective against Asian strain of CHIKV with an IC_{50} of 15.62 μM [27]. This study led to an interesting finding as the aqueous ethanolic extract of *Hyptis suaveolens* found to be more selective towards inhibition of Asian strain of CHIKV when compared with ribavirin. This inhibitory activity might be due to the presence of pentacyclic triterpenoids as major constituent. Further study might focus on purification of active constituents to explore novel scaffolds with antichikungunya activity.

In a recent study, an immunofluorescence-based screening was performed to identify potential inhibitors of CHIKV using a highly purified natural product compound library. Out of these focused library 44 compounds exhibiting >70 % inhibition of CHIKV infection were identified as positive hits. Harringtonine (**21**), (Fig. 10), a cephalotaxine alkaloid, displayed an EC_{50} 0.24 μM with minimal cytotoxicity [28]. In addition to its potent anti-CHIKV activity, time-of-addition studies, cotreatment assays etc. highlighted that harringtonine inhibit an early stage of CHIKV replication cycle by affecting viral protein expression [28]. The highly selective inhibitory nature of harringtonine as well as its inhibitory activity against sindbis virus, another alphavirus makes it a blockbuster candidate for further rational drug design efforts against CHIKV and other alphaviruses.

CHIKV NSP2 (non-structural protease 2) is one of the emerging target to discover novel inhibitors towards this emerging alphavirus. High throughput screening of 3040 molecules led to identification of a natural compound (**22**), (Fig. 11) which partially blocks NSP2 and CHIKV replication [29]. This study could further open up an opportunity to develop novel CHIKV NSP2 inhibitors from a natural product.

Also recently, a focused library of 356 compounds including natural products and clinically approved drugs were screened against EGFP and Rluc marker genes expressed by the CHIKV replicon. The 5, 7-dihydroxyflavones apigenin

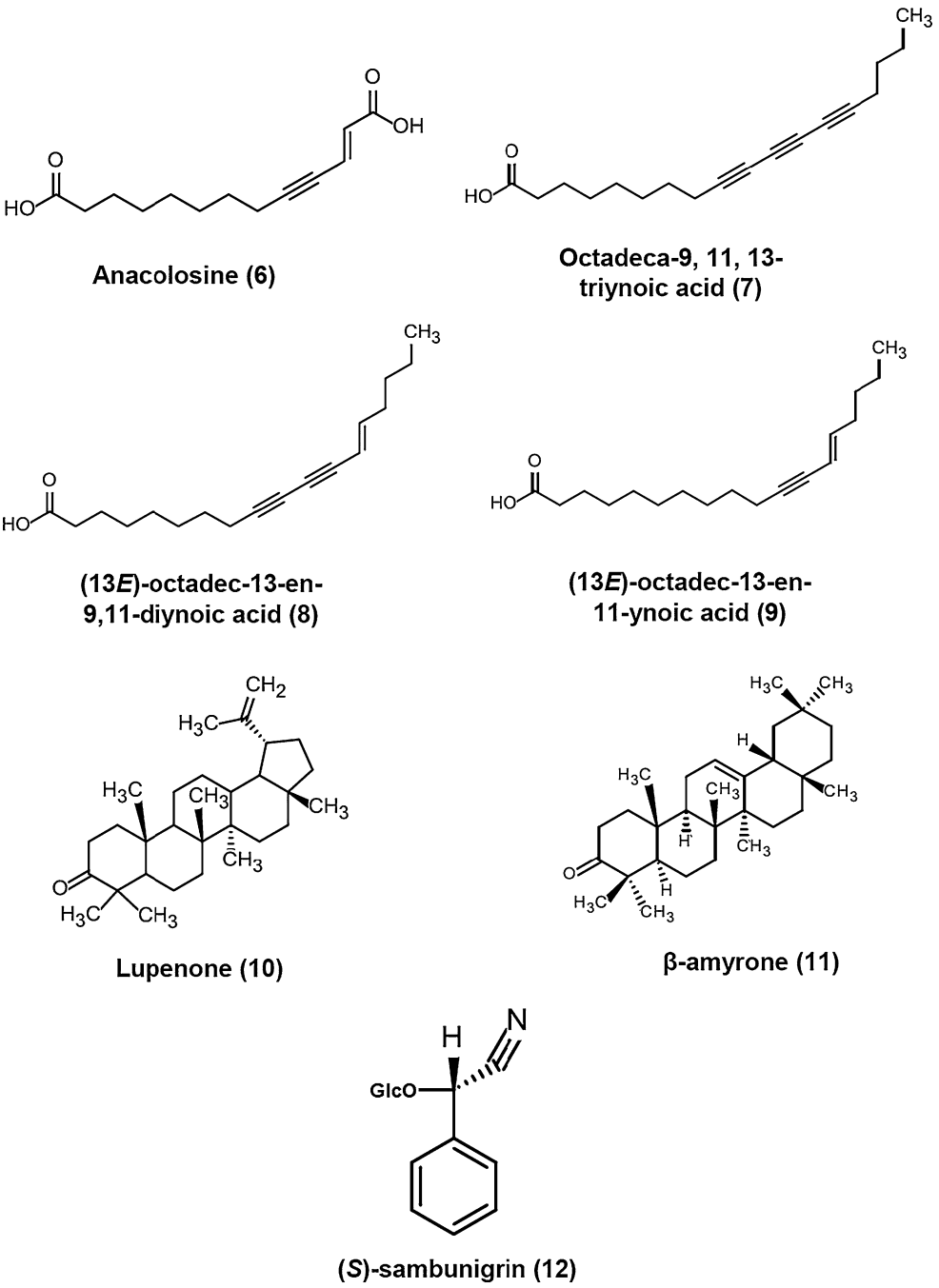

Fig. 7 Structural representation of anacolosine (**6**), octadeca-9,11,13-triynoic acid (**7**), (13*E*)-octadec-13-en-9,11-diynoic acid (**8**), (13*E*)-octadec-13-en-11-ynoic acid (**9**), lupenone (**10**), β-amyrone (**11**), and (*S*)-sambunigrin (**12**)

(**23**), chrysin (**24**), naringenin (**25**) and silybin (**26**) (Fig. 12) were found to suppress activities of EGFP and *Rluc* (*Renilla* luciferase) marker genes expressed by the CHIKV replicon (Table 4) [30]. Further these compounds also found to inhibit genome-replication of Semliki Forest virus (SFV), another alpha virus. Silybin (**28**) found to inhibit the entry of SFV into the host cell [30]. The antiviral activity of these compounds on *Rluc* gene confirmed that these molecules can inhibit genome replication of CHIKV and other alphaviruses [30]. Thus development of small molecule inhibitors using the pharmacophoric features of these

Table 2 Antiviral activities of compounds **6**–**12** in vero cells against CHIKV [24]

Compounds	CC_{50} vero cells (μM)	EC_{50} CHIKV (μM)
Compound **6**	>420	>420
Compound **7**	30	>30
Compound **8**	23	>23
Compound **9**	30	>30
Compound **10**	>235	77 ± 26
Compound **11**	>235	86 ± 9
Compound **12**	>426	>426

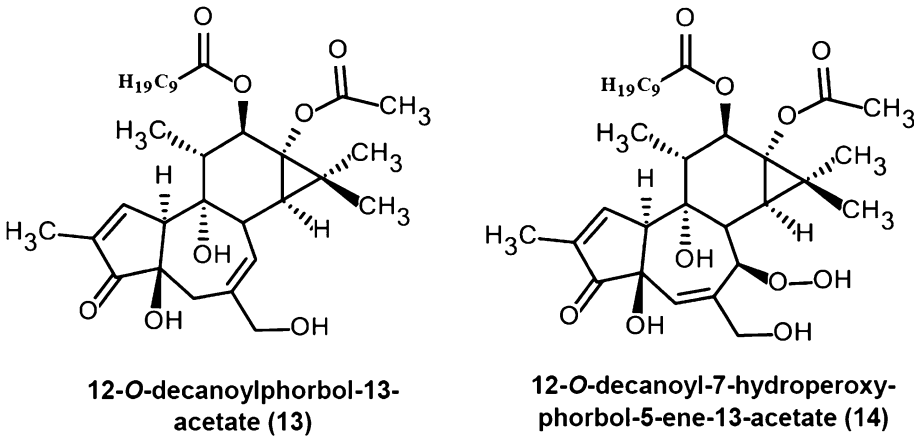

Fig. 8 2D structural representation of 12-*O*-decanoylphorbol-13-acetate (**13**) and 12-*O*-decanoyl-7-hydroperoxy-phorbol-5-ene-13-acetate (**14**) isolated from the leaves of *Croton mauritianus*. R3=R4=C_9H_{19}

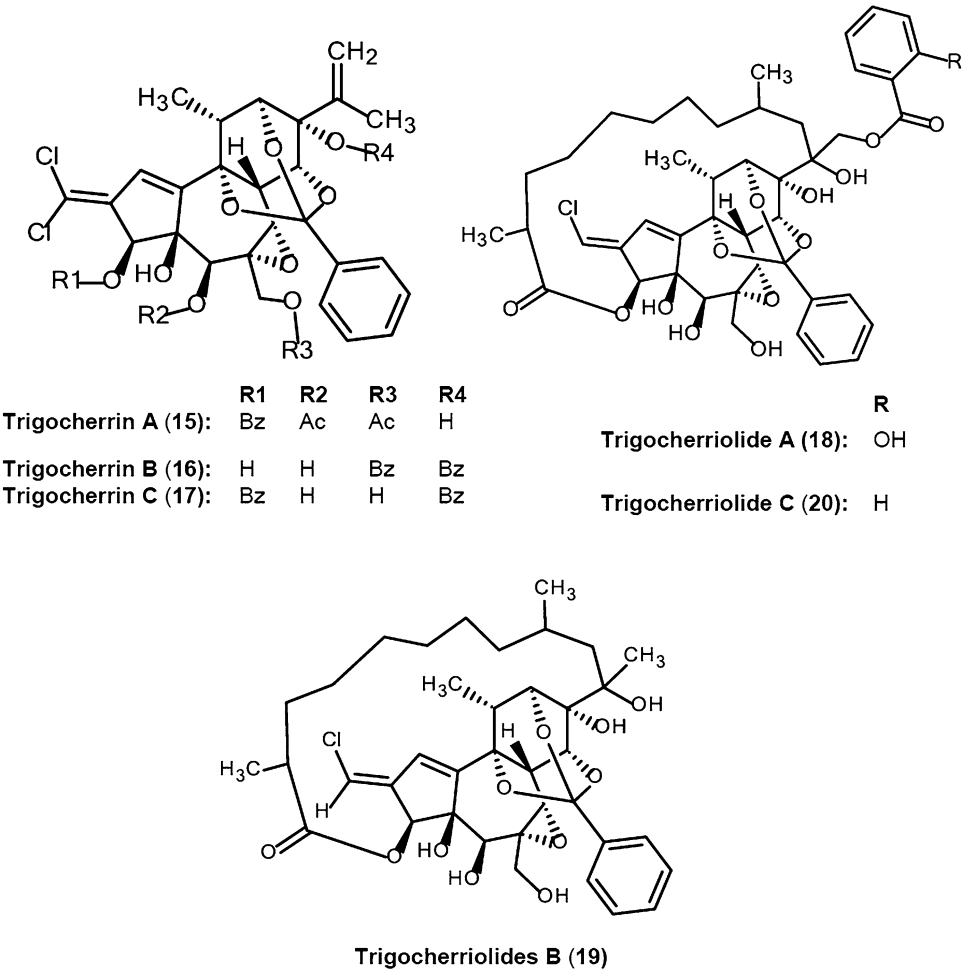

Fig. 9 Structural representation of daphnane diterpenoid orthoesters isolated from *Trigonostemon cherrieri*

compounds might lead to development of new replication inhibitor against CHIKV. Whereas, the structural and pharmacophoric feature of silybin (**28**) will be helpful in the development of entry inhibitors targeting CHIKV and other alphaviruses.

In a different report, two new daphnane diterpenoid orthoesters, trigocherrierin A (**27**), (Fig. 13) and trigocherriolide E were isolated from the leaves of *Trigonostemon cherrieri* exhibited anti-CHIKV activity in virus cell-based assay [31]. Trigocherrierin A displayed

Table 3 Anti-CHIKV activities of compounds **15–20** in virus cell based assay [26]

Compounds	CC_{50} vero cells (μM)	EC_{50} CHIKV (μM)
Compound **15**	35 ± 8	1.5 ± 0.6
Compound **16**	93 ± 3	2.6 ± 0.7
Compound **17**	23.1 ± 0.6	3.0 ± 1.2
Compound **18**	4.6 ± 0.8	1.9 ± 0.6
Compound **19**	5.3 ± 0.2	2.5 ± 0.3
Compound **20**	10.5 ± 0.1	3.9 ± 1.0

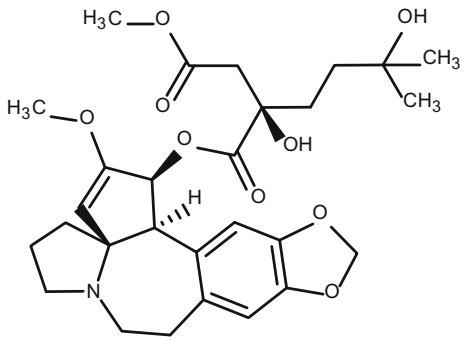

Fig. 10 Structural representation of harringtonine (**21**), a cephalotaxine alkaloid which displayed significant inhibitory activity against CHIKV [28]

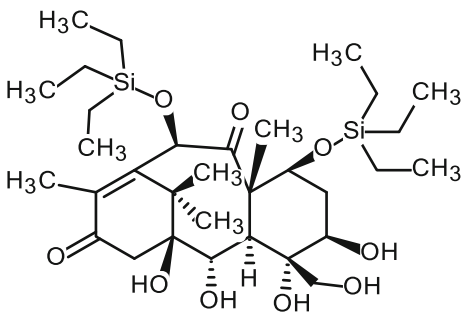

Fig. 11 Chemical representation of compound **22** which displayed inhibitory activity against CHIKV NSP2 [29]

strongest anti-CHIKV activity with EC_{50} 0.6 ± 0.1 μM and selectivity index (SI) = 71.7 [31].

In another unique study, bioassay guided purification of an EtOAc extract of the whole plant of *Euphorbia amygdaloides* ssp. *semiperfoliata* led to identification of a new jatrophane ester (**38**), (Fig. 14) which exhibited potent and selective inhibitory activity against CHIKV with an EC_{50} of 0.76 μM [32]. Findings reported from this exploration can be further continued with structure activity relationship study to develop more potent anti-CHIKV inhibitors by providing correct substitutions on the jatrophane skeleton.

Epigallocatechin-3-gallate (EGCG) (**29**), (Fig. 15), one of the major component of green tea displayed several biological activities such as HIV [33], cancer [34], fatigue syndrome [35] etc. Recent antiviral examination of EGCG displayed antiviral activity of EGCG against CHIKV. EGCG inhibited CHIKV infection in vitro by blocking the entry of CHIKV Env-pseudotyped lentiviral vectors and inhibiting CHIKV attachment [36]. Thus EGCG might be used as a structural template to design potent small molecule inhibitors targeting CHIKV.

Another antimalarial natural product, quinine (**30**), (Fig. 16) displayed significant anti-CHIKV activity with an IC_{50} 0.1 μg/ml at a concentration less than chloroquine (IC_{50} = 1.1 μg/ml) [37].

As a closing remark, the current efforts made to identify novel natural products against CHIKV is still insufficient and further research is highly encouraged towards either the discovery of novel leads or optimization of the currently identified compounds. This report demonstrated various potential chemical entities/scaffolds from natural sources; such information could assist medicinal chemists towards the design of optimized and more potent inhibitors against CHIKV.

Conclusions

During last 3 years, exploring several natural products as potential antivirals targeting CHIKV has gradually increased. Several interesting scaffolds with moderate to potent activity against CHIKV were reported, however, due to the neglected nature of the disease, less efforts were reported in order to optimize novel scaffolds identified from natural products in order to develop potent and selective inhibitors with an increased potency and ADME profile. Furthermore, the majority of the inhibitors were identified using in vitro cell-based assays, hence, identification of enzyme specific inhibitor targeting CHIKV is still a major challenge. As a result, till date, a very small amount of chemical space containing natural products have been explored in order to identify potent anti-CHIKV agents. With the advancement in assay techniques, future efforts might be directed towards identification of novel anti-CHIKV agents targeting specific structural/non-structural proteins using novel scaffolds identified from natural products. Natural product inspired small molecule inhibitors might prove a cornerstone in the hectic development process of drug candidates against CHIKV due to their low toxicity profile. Using modern state of the art

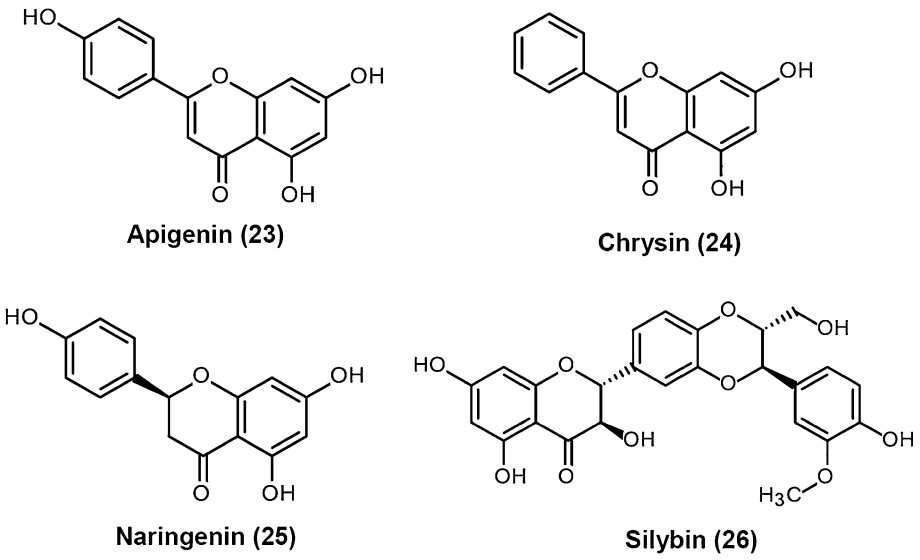

Fig. 12 2D structural representations of compound **23**-**26** which displayed antiviral activities against EGFP and Rluc marker genes expressed by the CHIKV [30]

Table 4 Antiviral activity of compound **25**–**28** against EGFP and *Rluc* marker genes expressed by the CHIKV [30]

Natural products	EGFP IC_{50} (μM)	Rluc IC_{50} (μM)
Apigenin (**23**)	22.5	28.3
Chrysin (**24**)	46.8	50.2
Naringenin (**25**)	25.8	30.0
Silybin (**26**)	71.1	59.8

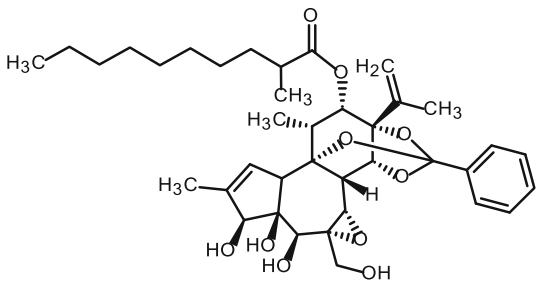

Fig. 13 2D structural representation of daphnane diterpenoid orthoester based CHIKV inhibitor, trigocherrierin A (**27**) [31]

computational approach the structural and pharmacophoric features of active natural products can be used in order to develop target specific inhibitors against CHIKV. The use of GRID computing and collaborative drug discovery efforts will play a crucial role in this process in order to speed up the discovery process. In conclusion, more effort from researchers towards the development of antiviral agents targeting CHIKV from natural products is highly

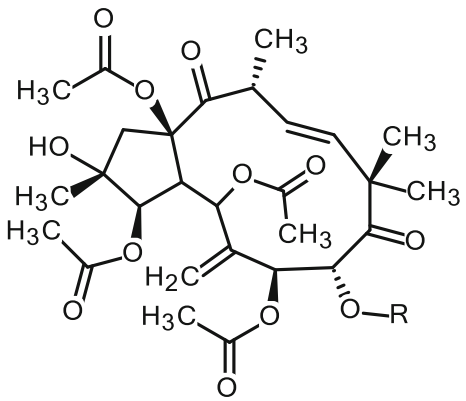

Fig. 14 Structural representation of a jatrophane ester (**28**) which exhibited selective inhibitory activity against CHIKV [32]. "**R**" represents tiglyloxy (Tig) group

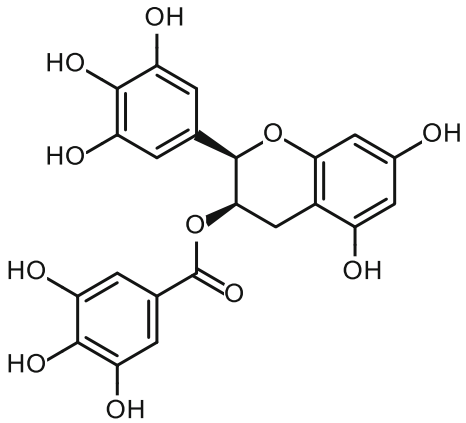

Fig. 15 2D structural feature of epigallocatechin-3-gallate (**29**)

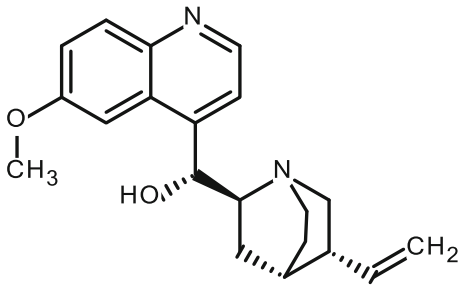

Fig. 16 Chemical representation of quinine (**30**), an antimalarial compound which displayed anti-CHIKV activity

encouraged. More advanced computer-assisted and molecular modelling approaches augmented with analytical and experimental techniques should be applied in order to optimize the activity of the currently discovered natural compounds.

Acknowledgements SB wish to thank School of Health Sciences, University of KwaZulu-Natal for providing financial support through scholarship in the academic year 2013/14.

Conflict of interest Authors declare there is no potential conflicts of interests.

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