Garcinol from *Garcinia indica* inhibits HIV-1 reverse transcriptase-associated ribonuclease H

Angela Corona1 | Sebastian Seibt2 | David Schaller3 | Rainer Schobert2 | Andrea Volkamer3 | Bernhard Biersack2 | Enzo Tramontano1,4

1Laboratorio di Virologia Molecolare, Dipartimento di Scienze della Vita e Dell’Ambiente, Università degli Studi di Cagliari, Monserrato, Italy
2Organic Chemistry Laboratory, University of Bayreuth, Bayreuth, Germany
3In Silico Toxicology and Structural Bioinformatics, Institute of Physiology, Charité-Universitätsmedizin Berlin, Berlin, Germany
4Istituto di Ricerca Genetica e Biomedica, Consiglio Nazionale delle Ricerche (CNR), Monserrato, Cagliari, Italy

**Correspondence**
Angela Corona, Laboratorio di Virologia Molecolare, Dipartimento di Scienze della Vita e Dell’Ambiente, Università degli Studi di Cagliari, Cittadella Universitaria di Monserrato S5554, 09042 Monserrato, Italy.
Email: angela.corona@unica.it
Bernhard Biersack, Organic Chemistry Laboratory, University of Bayreuth, Universitätsstrasse 30, 95440 Bayreuth, Germany.
Email: bernhard.biersack@yahoo.com

**Funding information**
Regione Autonoma della Sardegna, Grant/Award Number: RASSR17032

**Abstract**
The bioactive components of *Garcinia indica*, garcinol (camboginol), and isogarcinol (cambogin), are suitable drug candidates for the treatment of various human diseases. HIV-1 RNase H assay was used to study the RNase H inhibition by garcinol and isogarcinol. Docking of garcinol into the active site of the enzyme was carried out to rationalize the difference in activities between the two compounds. Garcinol showed higher HIV-1 RNase H inhibition than the known inhibitor RDS1759 and retained full potency against the RNase H of a drug-resistant HIV-1 reverse transcriptase form. Isogarcinol was distinctly less active than garcinol, indicating the importance of the enolizable β-diketone moiety of garcinol for anti-RNase H activity. Docking calculations confirmed these findings and suggested this moiety to be involved in the chelation of metal ions of the active site. On the basis of its HIV-1 reverse transcriptase-associated RNase H inhibitory activity, garcinol is worth being further explored concerning its potential as a cost-effective treatment for HIV patients.

**Keywords**
antiviral drugs, garcinol, *Garcinia indica*, HIV, RNase H

1 | INTRODUCTION

Human immunodeficiency virus comprising type 1 and type 2 (HIV-1 and HIV-2) is a widespread virus that infected ca. 37.9 million people (among them ca. 2.1 million children below 15 years) and resulted in 770,000 deaths worldwide in late 2018 (www.unaids.com). There is neither vaccine for nor cure of HIV infection until today, and there is no effective approach to eradicate HIV-1 integrated in latently infected tissue reservoirs.[1,2] The progression of HIV infection can lead to the acquired immunodeficiency syndrome (AIDS) that has killed about 35 million people worldwide since the first known infections in the 1980s (www.unaids.com). Treatment of HIV infections is conducted through highly active antiretroviral therapy (HAART), which mainly includes inhibitors of HIV reverse transcriptase (RT;
inhibition of its DNA polymerase subunit RDDP/RNA-dependent DNA polymerase), inhibitors of HIV integrase (IN), and inhibitors of HIV protease. However, side effects of these drugs, together with the emergence of drug resistance, have become an increasing clinical problem.\cite{3-5} Coinfection with other infectious diseases such as leishmaniasis or hepatitis B (HBV) poses another threat also to people living in underdeveloped countries.\cite{6,7}

The identification of new viral drug targets can help to overcome viral resistance mechanisms. Besides its DNA polymerase unit, the HIV RT enzyme also harbors an RNase H domain, which, on the one hand, degrades the RNA strand of the RNA/DNA intermediate during replication in an unspecific way. On the contrary, RNase H catalyzes specific hydrolysis of RNA primers during the biosynthesis of integration-competent proviral DNA.\cite{8} The active site of RNase H contains four conserved negatively charged amino acids (DEDD motif) with two Mg$^{2+}$ ions required for catalysis, that is, for hydrolysis of phosphate esters of target RNAs. Interestingly, the Mg$^{2+}$ ions could be replaced by Mn$^{2+}$, conserving a functional enzyme, whereas the exchange for Ca$^{2+}$ ions inhibited the enzyme.\cite{9,10} Several RNase H inhibitors have been identified over the last few years. Besides competitive inhibitors of the active site of HIV (and of HBV) RNase H acting via coordination of the Mg$^{2+}$ ions in the active site, allosteric inhibitors leading to protein destabilization were described as well.\cite{11} Various natural products such as triterpenes (betulinic acid), lignans (schisandrin B), and prenylated acylphloroglucinols were identified as RNase H inhibitors.\cite{12-14} Moreover, the HIV-1 RT-associated RNase H domain displays a high degree of conservation among naive and drug-experienced patients, and its inhibition could overcome RT resistance and might pave the way to new treatment options.\cite{15,16}

Considering the critical healthcare situation in poor countries and the emergence of drug resistance, new cost-effective drugs and treatment options for viral infectious diseases are needed (www.dndi.org). Natural products from tropical plants have great potential as easily available drugs against infections and tropical diseases.\cite{17,18}

For ages, traditional folk medicine such as Ayurveda and Traditional Chinese Medicine have applied numerous plant-derived drugs for the treatment of various diseases.\cite{19-21} Garcinia indica (the kokum tree) is a tree growing along the sunny and fertile western coast of India. The plum of the kokum tree is a popular sour spice in the Konkan region and used for the preparation of local sharbats, curries, and dishes such as “sol kadhi” known to tourists and locals alike. In addition, Ayurveda practitioners apply kokum-based drugs for the treatment of edema and infections.\cite{22,23} The fruit rind of dried kokum plums contains significant amounts (ca. 2.5%) of garcinol (also called cambogin in the literature) and, to a lesser extent, its isomer isogarcinol (cambogin), which belong to the type B polycyclic poly-prenylated acylphloroglucinols or polyprenylated benzophenones (Figure 1).\cite{24,25} Both garcinol and isogarcinol showed a plethora of biological activities against cancer, infections, and inflammatory diseases.\cite{26,27} The activities of garcinol against various in vivo tumor models were thoroughly investigated and the compound was well tolerated by laboratory animals at active doses.\cite{28-30} In addition, garcinol was identified as a natural histone acetyltransferase (HAT) inhibitor and it suppressed the lysine acetylation of the influenza A viral nucleoprotein.\cite{31} Histone acetylation/deacetylation is also an important process in HIV-infected cells concerning the formation of latent infection states. Isogarcinol and its semisynthetic derivative LTK-14 suppressed HIV transcription based on HAT p300

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{FIGURE_1.png}
\caption{Structures of garcinol, isogarcinol, and the reference compounds used in this study}
\end{figure}
inhibition.\textsuperscript{32,33} Given these promising preliminary findings about the antiviral activities of garcinol and isogarcinol, we conducted further investigations to identify new HIV targets of these natural products.

In the present report, we disclose promising results of garcinol as a natural product to inhibit the RNase H domain of the HIV-1 reverse transcriptase protein.

2 RESULTS AND DISCUSSION

Garcinol and isogarcinol were tested for their HIV-1 RT-associated RNase H and DNA polymerase inhibitory activities (Table 1). Their activities were compared with the activities of RDS1759 and efavirenz as positive controls. Garcinol showed significant inhibition of the wild-type HIV-1 RNase H (IC\textsubscript{50} = 6.6 ± 2.1 µM), comparable to our previously published synthetic compound \textsuperscript{13} and it was slightly more active than the positive control RDS1759.\textsuperscript{16,34} The activity of garcinol lies in the activity range of other natural prenylated acylphloroglucinol compounds isolated from Hypericum scruglii plants growing on Sardinia.\textsuperscript{14} Isogarcinol was found to be distinctly less active than garcinol and RDS1759. Isogarcinol is the pyrano isomer of garcinol and it seems that the tris-β-diketone moiety of garcinol is necessary for a high inhibitory activity against RNase H. Garcinol also retained full inhibitory potency against the RNase H function of the drug-resistant K103N-Y181C reverse transcriptase form in contrast to RDS1759 and compound \textsuperscript{13}, which showed distinctly lower activities against the mutant form than against the wild-type enzyme. Although isogarcinol was also less active than garcinol against the mutant enzyme, it is interesting to note that isogarcinol was ca. twice as active against the mutant form as against the wild-type form. In addition, isogarcinol showed moderate inhibitory activities against the tested HIV-1 RDDP enzymes, whereas garcinol was way less active than isogarcinol. Hence, garcinol showed considerable selectivity for the HIV-1 RNase H enzymes when compared with the HIV-1 RDDP enzymes used in this study.

To rationalize the observed difference in inhibitory efficacies of garcinol and isogarcinol concerning the HIV-1 RNase H enzymatic activity, molecular docking was performed for both compounds in the RNase H domain present in the PDB structure 4GAQ.\textsuperscript{35} Interestingly, garcinol features an enol conjugated to two carbonyl groups, which gives rise to several keto–enol tautomers, whose deprotonated conjugate bases are identical mesomers. To consider this, all likely tautomers and protonation states were enumerated and docked using functionalities from the OpenEye toolkit 2020.2.0.

![FIGURE 2 Predicted docking pose of garcinol in the HIV RNase H domain of the PDB structure 4GAQ.\textsuperscript{35} Ligand carbon atoms are colored in orange, protein carbon atoms in white, all oxygen atoms in red, and all nitrogen atoms in blue. Highlighted residues (sticks) are involved in interactions with garcinol or are chelating the manganese ions. Interaction types: Magenta cones—manganese binding location, red star—negative ionizable, red arrows—hydrogen bond acceptors, green arrows—hydrogen bond donors, yellow spheres—hydrophobic contact, blue spheres—manganese ions](image-url)

| Compound | HIV-1 RT RNase H IC\textsubscript{50} (µM) | HIV-1 RT RNase H K103N-Y181C IC\textsubscript{50} (µM) | HIV-1 RT RDDP IC\textsubscript{50} (µM) | HIV-1 RT RDDP K103N-Y181C IC\textsubscript{50} (µM) |
|----------|----------------------------------------|-----------------------------------------------|---------------------------------|-----------------------------------------------|
| Garcinol  | 6.6 ± 2.1                              | 8.4 ± 0.4                                     | 46.7 ± 10.0                     | 63.7 ± 7.2                                    |
| Isogarcinol | 29.0 ± 1.4                              | 15.9 ± 7.8                                    | 30.3 ± 1.1                      | 20.7 ± 1.6                                    |
| RDS1759  | 8.7 ± 3.1                              | 14.6 ± 2.3                                    | >50                              | -                                             |
| \textsuperscript{13} | 5.8 ± 1.3                              | 20.4 ± 1.1                                    | >50                              | -                                             |
| Efavirenz | -                                      | -                                             | 0.051 ± 0.007                   | 0.292 ± 0.75                                  |

Note: RDS1759, compound \textsuperscript{13}, and efavirenz were applied as positive controls.

\*Compound concentration required to reduce the HIV-1 RT-associated RNase H activity or RDDP activity by 50%.
of the cocrystallized Mn$^{2+}$ ions in the active site by the hydroxylate and an adjacent carbonyl group (Figure 2). In addition, we observed hydrogen bonds with ALA446, ARG448, ASN474, and ARG557, also proven to be involved in compound 13 binding as well as hydrophobic contacts with ALA445 and ALA538.[16] The critical deprotonatable hydroxyl group of garcinol involved in chelation of the Mn$^{2+}$ ions is not present in isogarcinol (Figures 1 and 2). Thus, the missing negative charge in isogarcinol may cause a weaker interaction with the Mn$^{2+}$ ions of the enzyme and, consequently, a decreased inhibitory activity of isogarcinol. In addition, the observed activity difference is also reflected by the MMFF94 binding enthalpy as calculated with LigandScout 4.4 (the lower the better), that is, $-181.50$ kcal/mol for the selected docking pose of garcinol (Figure 2) and $-94.34$ kcal/mol for the lowest energy docking pose of isogarcinol.

3 | CONCLUSIONS

Garcinol showed a significant HIV-1 RT-associated RNase H inhibitory activity, and docking calculations suggest the relevance of the metal ion-chelating enolizable tris-β-diketone fragment of garcinol, which is absent in the less active isogarcinol due to the pyran ring closure. Thus, the antiviral activity of garcinol is worth being further explored in ex vivo and in vivo models, with the perspective of its formulation as a cost-effective HIV treatment, in particular, in cases where resistance of RT occurred. As already mentioned above, previous in vivo studies concluded that garcinol is a safe and well-tolerated drug candidate.[28–30] These promising in vivo results warrant further investigation of garcinol as a potential antiviral drug candidate although in vitro assays with tumor cell lines revealed considerable cytotoxicity for it and its manifold antitumor activities are indeed well described.[28,30,36,37] Furthermore, a chemical fine-tuning of garcinol might improve its affinity for HIV-1 RT-associated RNase H and related viral ribonucleases with Mg$^{2+}$-dependent active sites. For instance, the exonuclease activity of coronavirus Nsp14 protein depends on Mg$^{2+}$ and can be a highly relevant target for such metal-chelating compounds in future studies.[38] In case of oral administration of garcinol, enteric coating formulations should be considered, as garcinol might otherwise isomerize to the less active isogarcinol under acidic conditions.

4 | EXPERIMENTAL

4.1 | General

Dried kokum plums (Garcinia indica) were purchased from Santulan Ayurveda GmbH (Munich, imported from Maharashtra, India). Garcinol (camboiginol) was isolated from dried kokum plums as a yellow solid according to literature procedures.[26] The dried kokum plums (500 g) were chopped, methanol (1 L) was added to the chopped plums, and the suspension was stirred with a KPG stirrer at room temperature for 24 h. The suspension was filtered, methanol (1 L) was added to the kokum residue, and the suspension was stirred again at room temperature for 24 h. The suspension was filtered and the combined methanol extracts were concentrated in vacuum. Water (1 L) was added to the concentrated extract and the aqueous solution was extracted with ethyl acetate (4 × 500 ml). The organic phases were dried over Na$_2$SO$_4$, filtered, and the filtrate was concentrated in vacuum. The obtained residue was purified by column chromatography (silica gel 60; ethyl acetate/n-hexane 3:7; v/v) and recrystallized from n-hexane. Yield: 5.5 g; yellow solid; R$_f$ = 0.37 (ethyl acetate/n-hexane 3:7); $^1$H NMR (nuclear magnetic resonance) (300 MHz, MeOD/1% TFA) δ 0.92 (3 H, s), 1.00 (3 H, s), 1.17 (3 H, s), 1.27 (3 H, s), 1.59 (3 H, s), 1.61 (3 H, s), 1.65 (3 H, s), 1.69 (3 H, s), 1.71 (3 H, s), 1.0–2.8 (12 H, m), 3.0–3.1 (1 H, m), 4.9–5.2 (3 H, m), 6.75 (1 H, d, J = 8.3 Hz), 7.05 (1 H, dd, J = 8.3 Hz, 2.1 Hz), and 7.26 (1 H, d, J = 2.1 Hz); $^13$C NMR (75 MHz, MeOD/1% TFA) δ 18.2, 18.4, 18.8, 21.7, 23.0, 26.3, 26.6, 26.8, 27.2, 29.2, 29.4, 30.7, 40.3, 44.7, 47.2, 47.6, 50.0, 52.8, 69.6, 88.4, 115.8, 116.4, 121.3, 123.1, 124.5, 126.7, 131.3, 134.1, 134.8, 135.6, 136.3, 151.1, 152.7, 173.8, 194.4, 196.4, and 208.1.

Isogarcinol was prepared as a colorless solid upon treatment of garcinol with diluted hydrochloric acid in toluene.[26] Garcinol (2.5 g, 4.25 mmol) was dissolved in toluene (24 ml) and concentrated HCl (1 ml) was added. After stirring at room temperature for 15 h, the reaction mixture was kept in a refrigerator. The precipitated solid was collected and recrystallized from acetonitrile. Yield: 800 mg (1.36 mmol, 32%); colorless solid; $^1$H NMR (300 MHz, deuterated dimethyl sulfoxide [DMSO-d$_6$]) δ 0.84 (3 H, s), 0.90 (3 H, s), 1.05 (3 H, s), 1.19 (3 H, s), 1.50 (3 H, s), 1.52 (3 H, s), 1.59 (3 H, s), 1.60 (3 H, s), 1.66 (3 H, s), 0.8–2.8 (12 H, m), 2.8–2.9 (1 H, m), 4.8–5.2 (3 H, m), 6.72 (1 H, d, J = 8.3 Hz), 6.93 (1 H, dd, J = 8.3 Hz, 2.2 Hz), and 7.13 (1 H, d, J = 2.2 Hz); $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 17.8, 17.9, 18.4, 21.0, 22.7, 25.6, 25.7, 26.1, 26.2, 28.3, 29.2, 30.5, 42.2, 42.7, 45.2, 45.6, 50.6, 51.1, 67.5, 86.3, 115.1, 117.4, 120.5, 121.9, 125.1, 125.3, 125.6, 132.5, 133.0, 133.2, 136.0, 151.4, 153.2, 170.9, 188.6, 198.3, and 207.0.

Analytical data of garcinol and isogarcinol correlated with published data and the compounds were used for the following biological studies.[32,39] The SYBYL line notation, together with selected activity data, is provided as Supporting Information. Efavirenz was purchased from Sigma-Aldrich. RDS1759 and compound 13 were kindly provided by Prof. Di Santo and Prof. Carcelli, and were prepared following literature procedures.[34,40]

4.2 | HIV1-RDDP-independent RNase H inhibition and RDDP inhibition assays

HIV-1 RT-associated RNase H inhibition and RDDP inhibition assays were carried out as described previously.[41,42] Briefly, anti-RNase H activity was measured in 100 µl reaction volume containing 50 mM Tris-HCl buffer pH 7.8, 6 mM MgCl$_2$, 1 mM dithiothreitol (DTT), 80 mM KCl, and HIV-1 RT. Reaction was started adding hybrid RNA/DNA 5′-GAUCUGAGCCUGCAGGCU-fluorescein-3′ (high-performance liquid chromatography [HPLC], dry, QC: Mass Check) (available from...
Metabion) and 5′-dabcyl-ACTCCCGAGTCGAC-3′ (HPLC, dry, QC: Mass Check) at a final concentration of 0.25 µM. The reaction mixture was incubated for 10 min at 37°C in a multilabel counter plate reader Victor 3 (Model 1420-051, Perkin Elmer), and the product was quantified at 490/528 nm (excitation/emission wavelength). The RT-associated RDDP activity was measured in 30 µl volume containing 60 mM Tris-HCl pH 8.1, 8 mM MgCl2, 60 mM KCl, 13 mM DTT, 100 µM dTTP, 5 nM RDDP. The reaction mixture was incubated for 30 min at 37°C. The enzymatic reaction was stopped by addition of EDTA. Reaction products were detected by picogreen addition and measured with a Victor 3 (Perkin Elmer) plate reader at 502/523 nm. All experiments were done in triplicate.

4.3 Molecular modeling

A query of the protein data bank for a high-resolution structure of the HIV-1 RNase H in complex with an active site inhibitor identified the 1.71 Å resolution structure 4QAG.[35,43] This structure was prepared for docking using OESpruce and OECheM (OpenEye toolkit 2020.2.0) by protonation at pH 7.4. OEDocking (OpenEye toolkit 2020.2.0) was used to dock garcinol and isogarcinol into the active site of the prepared HIV RNase H domain. SMILES notations of both compounds were taken from OEQuacpac (OpenEye toolkit 2020.2.0), and conformations for each tautomeric state were assigned using OEOmega (OpenEye toolkit 2020.2.0). The hybrid protocol was chosen for docking employing the cococrystallized ligand of 4QAG to bias ligand placement, which finally led to the generation of 20 docking poses per compound. Afterward, docking poses were energetically minimized inside the RNase H binding pocket using LigandScout 4.4 (license kindly provided by Prof. G. Wolber) and the MMFF94s force field.[45,46]

ACKNOWLEDGMENTS

The authors thank Nadine Beck for assistance in the preparation of garcinol and isogarcinol. Angela Corona and Enzo Tramontano were supported by Regione Autonoma della Sardegna (RAS) (LR 07/2017, annualità 2017) grant no. RASSR17032. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

ORCID

Angela Corona https://orcid.org/0000-0002-6630-8636
Andrea Volkamer https://orcid.org/0000-0002-3760-580X
Bernhard Biersack https://orcid.org/0000-0001-7305-346X
Enzo Tramontano https://orcid.org/0000-0002-4849-0980

REFERENCES

[1] J. Cohen, Science 2020, 367, 611.
[2] L. J. Henderson, L. B. Reoma, J. A. Kovacs, A. Nath, J. Virol. 2020, 94(3), e00375-19.
[3] L. Menéndez-Arias, Antivir. Res. 2013, 98, 93.
[4] N. Stella-Ascariz, J. R. Arribas, R. Paredes, J. Z. Li, J. Infect. Dis. 2017, 216, 5847.
[5] R. K. Gupta, J. Gregson, N. Parkin, H. Haile-Selassie, A. Tanuri, L. Andrade Forero, P. Kaleebu, C. Watera, A. Aghokeng, N. Mutenda, J. Dzangare, S. Hone, Z. Z. Hang, J. Garcia, Z. Garcia, P. Marchorro, F. Beteta, A. Giron, R. Hamers, S. Inzaule, I. M. Frenkel, M. H. Chung, T. de Oliveira, D. Pillay, K. Naidoo, A. Kharsany, R. Kugathasan, T. Cutino, G. Hunt, S. A. Rios, M. Doherty, M. R. Jordan, S. Bertagnolli, Lancet Infect. Dis. 2017, 18, 346.
[6] J. Alvar, P. Aparicio, A. Aseffa, M. Den Boer, C. Canavate, J.-P. Dedet, L. Gradoni, R. Ter Horst, R. López-Vélez, J. Moreno, Clin. Microbiol. Rev. 2008, 21, 334.
[7] K. P. Singh, M. Crane, J. Audsley, A. Avihingsanon, J. Sadaeusse, S. R. Lewin, AIDS 2017, 31, 2033.
[8] S. F. Le Grice, J. Biol. Chem. 2012, 287, 40850.
[9] M. Nowotny, W. Yang, EMBO J. 2006, 25, 1924.
[10] E. Rosta, W. Yang, G. Hummer, J. Am. Chem. Soc. 2014, 136, 3137.
[11] E. Tramontano, A. Corona, L. Menéndez-Arias, Antiviral Res. 2019, 171, 104613.
[12] F. Esposito, C. Sanna, C. del Vecchio, V. Cannas, A. Venditti, A. Corona, A. Bianco, A. M. Serrilli, L. Guarcini, C. Parolin, M. Ballero, E. Tramontano, Pathog. Dis. 2013, 68, 116.
[13] L. Xu, N. Grandi, C. del Vecchio, D. Mandas, A. Corona, D. Piano, F. Esposito, C. Parolin, E. Tramontano, J. Microbiol. 2015, 53, 288.
[14] C. Sanna, M. Scognamiglio, F. Fiorentino, A. Corona, V. Graziani, A. Caredda, P. Cortis, M. Montisci, E. R. Ceresola, F. Canducci, F. Poli, E. Tramontano, F. Esposito, PLOS One 2018, 13, e0195168.
[15] A. Schneider, A. Corona, I. Spöring, M. Jordan, B. Buchholz, E. Maccioni, R. di Santo, J. Bodem, E. Tramontano, B. M. Wöhrli, Nucleic Acids Res. 2016, 44, 2310.
[16] A. Corona, E. Ballana, S. Distinto, D. Rogolino, C. D. Vecchio, M. Carcelli, R. Badia, E. Riveira-Munoz, F. Esposito, C. Parolin, J. A. Esté, N. Grandi, E. Tramontano, Viruses 2020, 12, 729.
[17] M. Butler, J. Nat. Prod. 2004, 67, 2141.
[18] R. K. Kesharwani, K. Misra, D. B. Singh, Asian Pac. J. Trop. Med. 2019, 12, 1.
[19] B. B. Aggarwal, A. B. Kunnumakkara, Molecular Targets and Therapeutic Uses of Spices: Modern Uses for Ancient Medicine, World Scientific Publishing Co. Pte. Ltd., Singapore, 2009.
[20] H. Yuan, Q. Ma, L. Ye, G. Piao, Molecules 2016, 21, 559.
[21] Z. Wang, L. Yang, J. Ethnopharmacol. 2016, 201, 113896.
[22] S. Padhye, A. Ahmad, N. Oswal, F. H. Sarkar, J. Hematol. Oncol. 2009, 2, 38.
[23] N. Saadat, S. V. Gupta, J. Oncol. 2012, 2012, 647206.
[24] R. Ciochina, R. B. Grossman, Chem. Rev. 2006, 106, 3963.
[25] A. M. Patel, S. B. Ezhava, I. S. Rathod, M. T. Chhabria, A. H. Patwari, R. Schobert, B. Biersack, S. Seibt, J. Microbiol. Pharmacother. Sci. 2015, 4, 595.
[26] B. Biersack, Effects of garcinol from kokum (Garcinia indica) on the prevention and treatment of cancer, in Critical dietary factors in Cancer Chemotherapy (Eds: M. F. Ullah, A. Ahmad), Springer International Publishing Switzerland, Cham, 2016.
[27] R. Schobert, B. Biersack, Chem. Biodiv. 2019, 16, e1900366.
[28] A. Ahmad, S. H. Sarkar, A. Aboukameel, S. Ali, B. Biersack, S. Seibt, Y. Li, B. Bao, D. Kong, S. Banerjee, R. Schobert, S. B. Padhye, F. H. Sarkar, Carcinogenesis 2012, 33, 2450.
[29] S.-H. Tu, Y.-S. Chiou, N. Kalyanam, C.-T. Ho, L.-C. Chen, M.-H. Pan, Food Funct. 2017, 8, 1067.
[30] N. Saadat, S. Akhtar, A. Goja, N. H. Razali, A. Geamanu, D. David, Y. Shen, S. V. Gupta, Nutr. Cancer 2018, 70, 1075.
[31] D. Hatakeyama, M. Shoji, S. Yamashio, R. Yoh, N. Ohmi, S. Takenaka, A. Saitoh, Y. Arakai, T. Komatsu, R. Nagano, M. Nakano, T. Noda, Y. Kawaoka, T. Kuzuhara, J. Biol. Chem. 2018, 293, 7126.
[32] K. Mantelingu, B. A. A. Reddy, V. Swaminathan, A. H. Kishore, N. B. Siddappa, G. V. P. Kumar, G. Nagashankar, N. Natesh, S. Roy, P. P. Sadhale, U. Ranga, C. Narayana, T. K. Kundu, Chem. Biol. 2007, 14, 645.

[33] G. Vansant, A. Bruggemans, J. Janssens, Z. Debyser, Viruses 2020, 12, 84.

[34] A. Corona, F. S. Di Leva, S. Thierry, L. Pescatori, G. Cuzzucoli Crucitti, F. Subra, O. Delelis, F. Esposito, G. Rigogliuso, R. Costi, S. Cosconati, E. Novellino, R. Di Santo, E. Tramontano, Antimicrob. Agents Chemother. 2014, 58, 6101.

[35] D. M. Himmel, N. S. Myshakina, T. Ilina, A. van Ry, W. C. Ho, M. A. Parniak, E. Arnold, J. Mol. Biol. 2014, 426, 2617.

[36] M. Farhan, A. Malik, M. F. Ullah, S. Afaq, M. Faisal, A. A. Farooqi, B. Biersack, R. Schobert, A. Ahmad, Int. J. Mol. Sci. 2019, 20, 800.

[37] P. Kopytko, K. Piotrowska, J. Janisiak, M. Tarnowski, Int. J. Mol. Sci. 2021, 22, 2828.

[38] Y. Ma, L. Wu, N. Shaw, Y. Gao, J. Wang, Y. Sun, Z. Lou, L. Yan, R. Zhang, Z. Rao, Proc. Natl. Acad. Sci. USA 2015, 112, 9436.

[39] R. Kaur, S. K. Chattopadhyay, S. Tandon, S. Sharma, Ind. Crops Prod. 2012, 37, 420.

[40] M. Carcelli, D. Rogolino, A. Gatti, N. Palà, A. Corona, A. Caredda, E. Tramontano, C. Pannecouque, L. Naesens, F. Esposito, Front. Microbiol. 2017, 8, 440.

[41] A. Corona, A. Schneider, K. Schweimer, P. Rösch, B. M. Wöhrl, E. Tramontano, Antimicrob. Agents Chemother. 2014, 58, 4086.

[42] A. Corona, J. Desantis, S. Massari, S. Distinto, T. Masaoka, S. Sabatini, F. Esposito, G. Manfroni, E. Maccioni, V. Cecchetti, C. Pannecouque, S. F. J. Le Grice, E. Tramontano, O. Tabarrini, ChemMedChem 2016, 11, 1.

[43] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, P. E. Bourne, Nucleic Acids Res. 2000, 28, 235.

[44] S. Kim, J. Chen, T. Cheng, A. Gindulyte, J. He, S. He, Q. Li, B. A. Shoemaker, P. A. Thiessen, B. Yu, L. Zaslavsky, J. Zhang, E. E. Bolton, Nucleic Acids Res. 2021, 49, D1388.

[45] G. Wolber, T. Langer, J. Chem. Inf. Model. 2005, 45, 160.

[46] T. A. Halgren, J. Comput. Chem. 1999, 20, 720.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: A. Corona, S. Seibt, D. Schaller, R. Schobert, A. Volkamer, B. Biersack, E. Tramontano. Garcinol from Garcinia indica inhibits HIV-1 reverse transcriptase-associated ribonuclease H. Arch. Pharm. 2021, e2100123. https://doi.org/10.1002/ardp.202100123