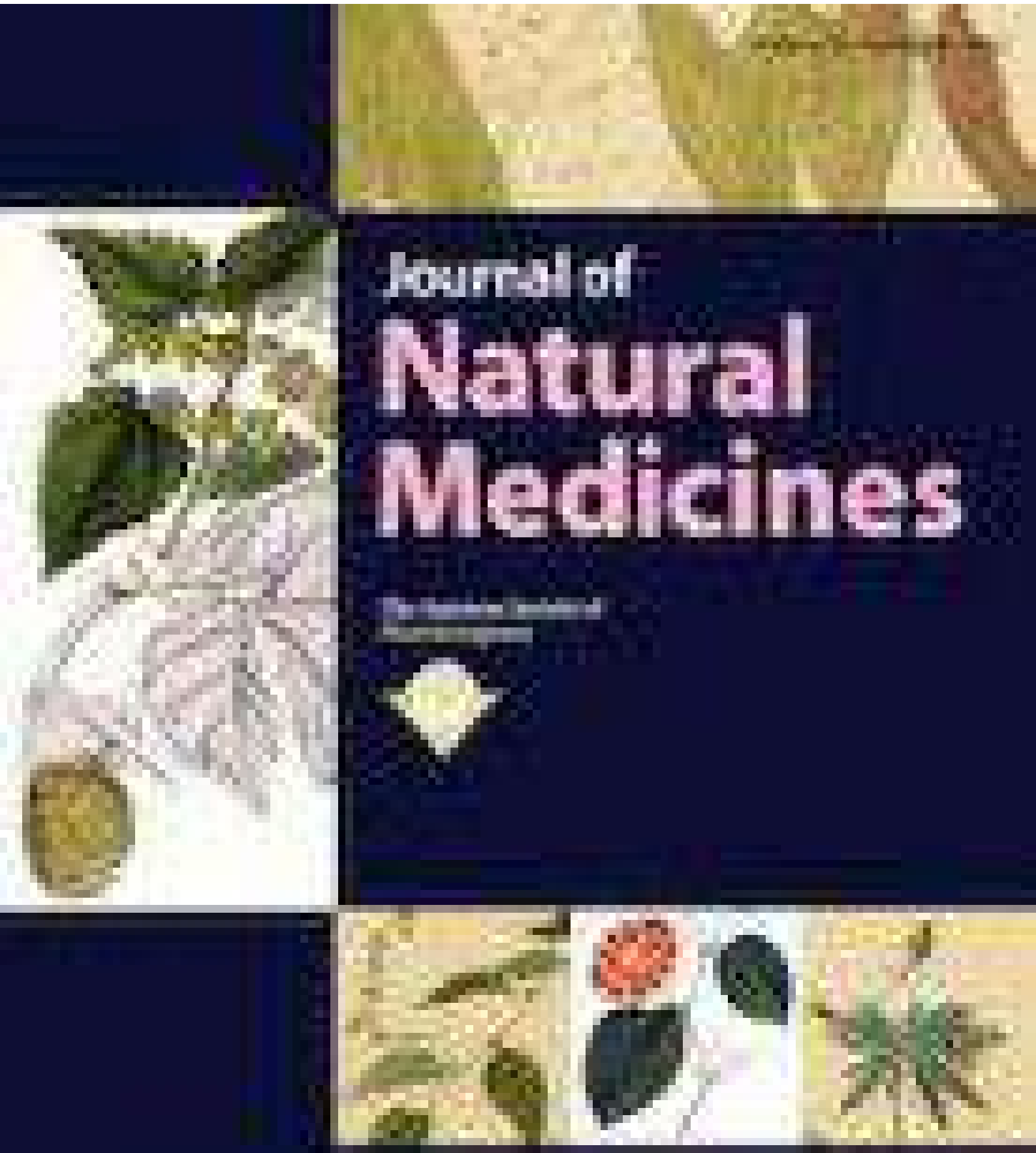

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NOTE

Pentacyclic triterpenes from the leaves extract of *Sandoricum koetjape*

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Abstract
Three new pentacyclic triterpenes, trivially named sandkoetjapic acids A–C (**1**–**3**), have been isolated from the leaves extract of *Sandoricum koetjape*, along with the known triterpenes 3-oxo-olean-12-en-29-oic (**4**), bryonolic (**5**), and bryononic (**6**) acids. The structures of the new triterpenes were determined mainly by NMR spectroscopic and mass spectroscopic data. The isolation of these pentacyclic triterpenes in the plant's leaves is for the first time. Preliminary biological evaluation of **1**–**6** was done against eight receptor tyrosine kinases (RTKs), including EGFR, HER2, HER4 (epidermal growth factor receptor), IGF1R, InsR (insulin receptor), KDR (kinase insert domain receptor), and PDGFRα/-β (platelet-derived growth factor receptor), and their inhibitory properties against β-lactamase. The results showed that none of them were active both as the inhibitors of these RTKs and β-lactamase.

Keywords Sandkoetjapics A-C · Pentacyclic triterpenes · *Sandoricum koetjape* · Meliaceae · Receptor tyrosine kinases (RTKs) · β-lactamase

Introduction

Sandoricum koetjape Merr. (Meliaceae), locally known as "Kecapi" or "Sentul", produces edible fruits and is an economically significant tree of South Asia [1]. Its traditional uses are very limited. The local Indonesian people have reported the aqueous preparation of the bark as a tonic for women after childbirth. In addition, the same herbal preparation is also used for colic and leukorrhea treatments [2]. Phytochemical studies of this plant revealed the presence of terpenoid derivatives, including sesquiterpenes [3], triterpenes [2–8], and limonoids [9–13]. These studies showed that the leaves were the source of the limonoids, while the terpenoids were isolated from the woods and bark of the plant. Some of the compounds have been studied for their anti-inflammatory [14], antifeedant [9], cytotoxicity and anticancer agent [2, 3, 7, 10], DNA polymerase ß-inhibitors [15], and inhibitor of NO production [13].

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Recently, we reported the limonoid and triterpene constituents from the fruits and bark of *S. koetjape* grown in Indonesia [16, 17]. In a continuation of these studies, we now report the presence of three new pentacyclic triterpenes **1**–**3**, named sandkoetjapics A–C, from the plant's leaves, along with three known triterpenes **4**–**6**. Preliminary biological evaluation of **1**–**6** as inhibitors of receptor tyrosine kinases (RTKs) and β-lactamase is also described.

Results and discussion

Compound **1** (Fig. 1) was isolated as a white powder, $[\alpha]^{20}_{D} = +10°$. The UV spectrum showed an absorption maxima at 212 nm, indicating that **1** has no conjugated double bonds. The IR spectrum displayed absorptions for the carbonyl groups of ketone (ν_{max} 1721 cm^{-1}) and carboxylic acid (ν_{max} 1685 cm^{-1}). This compound exhibited a negative quasi-molecular ion in the HRESI-TOF spectrum at *m/z* 453.3381, consistent with the molecular formula $C_{30}H_{46}O_3$ (calcd. *m/z* for $C_{30}H_{45}O_3^-$ 453.3374) (DBE = 8). The NMR spectra (Tables 1 and 2) displayed seven methyl proton signals (δ_H 1.09, 1.03, 1.03, 0.96, 0.95, 0.93, 0.74), a ketone group (δ_C 218.1), and a carboxylic acid (δ_C 180.3) group. These mass and NMR data suggest that **1** is a pentacyclic triterpene in which one of the methyl groups is modified

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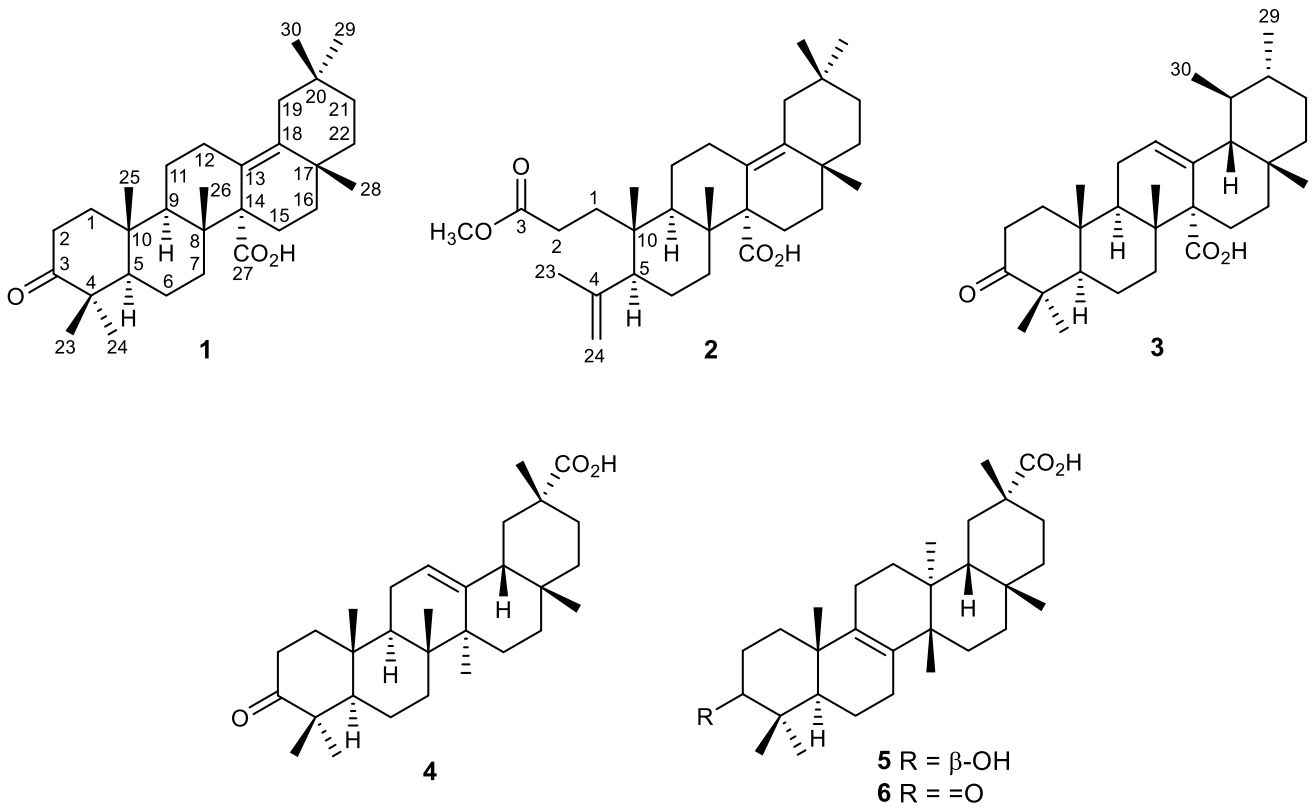

Fig. 1 Structures of pentacyclic triterpenes **1**–**6** from the leaves of *S. koetjape*

to a carboxylic acid group. The ^{13}C NMR spectrum also showed the presence of tetrasubstituted alkene signals (δ_C 138.0, 128.6), suggesting that **1** can be either multiflorane or olea-13(18)-en type. The presence of the HMBC correlations (Fig. 2) from the isolated methylene proton signals (δ_H 2.36, 1.71, H_2-19) to both the tetrasubstituted alkene carbon signals (δ_C 138.0, C-18; 128.6, C-13) is consistent with **1** as the olea-13(18)-en derivative. This was corroborated by the HMBC correlation between the C-18 signal and only one methyl signal (δ_H 1.03, H_3-28). No HMBC correlation was observed between any methyl proton signals and the C-13 signal, indicating that the carboxylic acid group is at C-27. Other HMBC correlations supporting structure **1** are shown in Fig. 2, and as expected, the C = O ketone group was placed at C-3. The stereochemistry of **1** was determined by the NOE correlations in the 2D-ROESY spectrum (Fig. 3). In aiding interpretation, the axial or equatorial position of the overlapping proton signals was predicted from the traces of the contour in the HSQC spectrum. The NOE correlations of H-5 and H_3-24, but not with H_3-23 and H_3-25, indicated that H-5 and H_3-25 are on the opposite side. Due to the very close of their chemical shift values, it is impossible to directly correlate the stereochemical relationship between H_3-25 and H_3-26. However, there were the NOE correlations for H_3-25/H-6_{ax} and H_3-26/H-15_{ax}/ H_3-28, indicating that H_3-26 and H_3-28 are on the same side of the olea-13(18)-en backbone, but on the opposite side from H-5 and H_3-24. Therefore, structure **1** was determined as 3-oxo-olean-13(18)-en-27-oic acid, trivially named sandkoetjapic acid A.

Compound **2**, trivially named as sandkoetjapic acid B, was also isolated as a white powder ($[\alpha]^{20}_D = -33°$) and has the molecular formula $C_{31}H_{48}O_4$ (found $C_{31}H_{48}O_4Na^+$ at *m/z* 507.3436, calcd. 507.3445). The UV spectrum of **2** was similar to that of **1**, indicating also that this compound has no conjugated double bonds. The IR spectrum displayed absorptions for the carbonyl groups of ester (ν_{max} 1739 cm^{-1}) and carboxylic acid (ν_{max} 1686 cm^{-1}). The NMR data (Tables 1 and 2) showed signals for a 2-isopropenyl group (δ_H 4.86, 4.63, 1.72; δ_C 147.2, 113.7, 23.4), a methyl ester (δ_H 3.64; δ_C 174.7, 56.4), a carboxylic acid group (δ_C 181.3), a tetrasubstituted alkene (δ_C 138.1, 128.6), and five methyl groups (δ_H 1.02, 0.96, 0.94, 0.86, 0.74). These mass and spectroscopic data suggest that **2** is a 3,4-*seco* derivative of **1**, in which the carboxylic acid formed is further modified to a methyl ester. In the HMBC spectrum, long-range ^{1}H-^{13}C correlations were found from the signals of two methylenes H_2-19 and H_2-12 (δ_H 2.37, 1.72 and 2.82, 22.9) to the alkenic carbon signals (δ_C 138.1, C-18; 128.6, C-13). Furthermore, no methyl proton signal was found to have HMBC correlation with the C-13 signal, indicating that the position of the

Table 1 ^{1}H NMR data of compounds **1**–**3** in $CDCl_3$

C No	1	2	3	3**
1	1.94 (*m*); 1.47 (*m*)	1.68 (*m*); 1.60 (*m*)	1.94 (*ddd*, 13.3, 7.7, 4.3) 1.57 (*br dt*, 13.3, 8.7)	1.78 (*ddd*, 13.1, 7.8, 4.4) 1.47 (*br dt*, 13.1, 9.0)
2	2.46 (2H, *m*)	2.30 (*m*); 2.22 (*m*)	2.50 (*ddd*, 16.1, 8.7, 7.7) 2.44 (*ddd*, 16.1, 8.7, 4.3)	2.49 (*ddd*, 16.1, 9.0, 7.8) 2.38 (*ddd*, 16.1, 9.0, 4.4)
5	1.45 (*m*)	2.02 (*dd*, 10.6, 2.3)	1.36 (*m*)	1.45 (*m*)
6	1.51 (*m*); 1.39 (*m*)	1.69 (*m*); 1.42 (*m*)	1.44 (2H, *m*)	1.35 (2H, *m*)
7	2.19 (*m*); 1.65 (*m*)	2.04 (*td*, 13.5, 3.2) 1.61 (*m*)	1.76 (*m*); 1.16 (*m*)	1.85 (*m*); 1.64 (*m*)
9	1.51 (*m*)	1.67 (*dd*, 12.9, 9.4)*	2.33 (*dd*, 11.2, 5.6)	2.79 (*dd*, 11.5, 5.2)
11	1.51 (*m*); 1.39 (*m*)	1.49 (*m*) 1.34 (*qd*, 12.9, 6.0)*	2.02 (*m*); 2.00 (*m*)	2.06 (*m*); 1.99 (*m*)
12	2.83 (*dd*, 15.0, 5.0) 2.28 (*m*)	2.82 (*dd*, 14.5, 4.2)* 2.29 (*ddd*, 14.5, 12.9, 5.3)*	5.59 (*br dd*, 4.6, 2.5)	5.69 (*br dd*, 5.0, 2.5)
15	1.94 (*m*); 1.75 (*m*)	1.97 (*dt*, 13.5, 3.2) 1.71 (*dd*, 13.5, 9.2)*	1.98 (*br d*, 13.6) 1.78 (*td*, 13.6, 4.3)	2.37 (*m*); 1.88 (*m*)
16	1.41 (*m*); 1.35 (*m*)	1.41 (*m*); 1.38 (*m*)	2.11 (*td*, 13.4, 3.6) 0.91 (*br d*, 13.4)	2.46 (*m*); 1.02 (*m*)
18	–	–	1.37 (*m*)	1.46 (*d*, 11.5)
19	2.36 (*br dd*, 13.8, 1.5) 1.71 (*br d*, 13.8)	2.37 (*br d*, 13.7) 1.72 (*br d*, 13.7)*	0.89 (*m*)	1.29 (*m*)
20	–	–	0.87 (*m*)	0.87 (*m*)
21	1.50 (*m*); 1.16 (*m*)	1.49 (*m*) 1.15 (*dm*, 12.8)	1.34 (*m*); 1.25 (*m*)	1.29 (2H, *m*)
22	1.34 (2H, *m*)	1.34 (2H, *m*)	1.42 (*m*); 1.25 (*m*)	1.44 (*m*); 1.29 (*m*)
23	1.03 (*s*)	1.72 (*s*)	1.03 (*s*)	1.02 (*s*)
24	1.09 (*s*)	4.86 (*br s*); 4.63 (*br s*)	1.06 (*s*)	0.95 (*s*)
25	0.95 (*s*)	0.86 (*s*)	1.05 (*s*)	0.98 (*s*)
26	0.93 (*s*)	0.94 (*s*)	1.07 (*s*)	1.10 (*s*)
28	1.03 (*s*)	1.02 (*s*)	0.84 (*s*)	0.97 (*s*)
29	0.74 (*s*)	0.73 (*s*)	0.79 (*br d*, 5.5)	0.78 (*d*, 6.3)
30	0.96 (*s*)	0.96 (*s*)	0.86 (*br s*)	1.10 (*d*, 6.0)
OCH_3	–	3.64 (*s*)	–	–

*Obtained from TOCSY-1D spectra

**Measured in pyridine-d_6

carboxylic acid group is also at C-27 as in **1**. As expected, the HMBC correlations also confirmed the attachments of the 2-isopropenyl group at C-5 and the ester propanoyl at C-10, as shown in Fig. 2. Some of the coupling constants of the overlapping proton signals were determined by analysis of its 1D-TOCSY spectra, which can identify the axial arientation of H-5, H-9, and H-15. In the 1D-ROESY spectra, the NOE correlations were found for H_3-25/H_3-26/H-15$_{ax}$/H_3-28. No NOE correlation was found between H-5 and H_3-25, but between H-5 and one of the methylenic alkene signal. These NOE correlations are consistent with **2** having the original structure of olean-13(18)-en. Therefore, structure **2** is determined to sandkoetjapic acid B. However, the presence of the methyl ester group in **2** might be an artifact due to the use of methanol in the extraction process.

Compound **3**, isolated as a white powder ($[\alpha]^{20}_{D} = +142°$), has the same molecular formula as **1** (*m/z* for $[M-H]^-$ 453.3360, calcd. for $C_{30}H_{45}O_3^-$ 453.3374). The UV and IR absorptions were also similar to those of **1**, indicating that **3** is an isomer of **1**. However, the IR spectrum also showed the absorption at ν_{max} 3026 cm^{-1}, suggesting the presence of a trisubstituted alkene group. The NMR data of **3** also resembled those of **1**, except that in **3** a trisubstituted alkenyl proton signal at δ_H 5.59 (Table 1) was observed. In addition, two methyl proton signals in **3** appeared as a doublet (δ_H 0.79) and a broad singlet (δ_H 0.86) in $CDCl_3$ or as a pair of doublets (δ_H 1.10, 0.78) in pyridine-d_5 (Table 1). Moreover, **3** has less than one quarternary aliphatic carbon, which is replaced by two methine groups (δ_H 0.89, 0.87; δ_C 39.6, 37.7). These mass and NMR spectroscopic data are consistent with **3** having a structure

Table 2 ^{13}C NMR data of compounds **1–3** in $CDCl_3$

C No	1	2	3	3*
1	39.3	33.9	39.3	39.8
2	34.1	28.4	34.0	34.5
3	218.1	174.7	218.0	217.0
4	47.2	147.2	47.1	47.4
5	54.1	49.7	54.6	55.1
6	21.3	24.6	19.7	20.2
7	34.9	34.5	36.0	36.8
8	41.6	41.3	39.8	40.1
9	51.5	42.2	45.9	46.5
10	37.1	39.8	36.6	37.1
11	21.3	21.3	22.9	23.7
12	26.5	26.5	128.4	128.1
13	128.6	128.6	133.2	135.1
14	59.2	59.3	55.8	56.8
15	23.5	23.2	22.4	23.3
16	37.0	37.1	28.9	29.9
17	34.7	34.7	33.7	34.3
18	138.0	138.1	60.3	61.0
19	38.9	38.9	37.7	38.2
20	34.2	34.2	39.6	40.0
21	35.3	35.4	30.3	31.0
22	39.2	39.2	40.8	41.6
23	21.2	23.4	21.3	21.7
24	27.0	113.7	27.0	27.1
25	16.3	20.3	16.4	16.6
26	18.4	18.7	18.1	18.6
27	180.3	181.1	180.9	178.0
28	23.9	24.0	29.0	29.7
29	24.0	23.9	17.8	21.7
30	24.0	32.4	21.4	18.8
OCH_3	–	51.6	–	–

*Measured in pyridine-d_6

of urs-12-en. In the HMBC spectrum, it was found that no methyl proton signal was correlated with the quarternary carbon signal of the trisubstituted alkene, indicating that the carboxylic acid group is also at C-27. As expected, the HMBC correlations also allowed the ketone group to be placed at C-3. Thus, **3** has the basic structure of 3-oxo-urs-12-en-27-oic acid. Other HMBC correlations supporting structure **3** are shown in Fig. 2. 1D-TOCSY measurements are also used to determine some ^1H-^1H coupling constants. The stereochemistry of **3** was determined by both 1D- and 2D-ROESY spectra measured in pyridine-d_5. These spectra clearly observed the presence of NOE enhancements for H_3-24/H-5/H-9 on one side and H_3-23/H_3-25/H_3-26 on the other side (Fig. 3). The same NOE enhancements were also observed for H_3-28/H-18/H_3-30/H_3-29. Furthermore, irradiation at δ_H 1.10 (H_3-26 and H_3-30) increased the signal intensities of H-15_{ax}, H-20, H_3-28, and H_3-29, confirming the stereochemical relationship between H_3-26 and H_3-28, and the axial orientation of H-20. These stereochemical assignments confirmed the structure **3** as 3-oxo-urs-12-en-27-oic acid, trivially named sandkoetjapic acid C. A literature search showed that **3** had been reported as the chemical transformation product of plectranthoic acid B [18].

The other three isolated compounds **4–6** were the known pentacyclic triterpenes and were determined as 3-oxo-olean-12-en-29-oic, bryonolic, and bryononic acids [5, 19], respectively, based on mass and NMR spectroscopic data.

This paper reports for the first time the presence of pentacyclic triterpenes in the leaves of *S. koetjape* growing in West Java, Indonesia. The leaves of *S. koetjape* collected in Malaysia, Thailand, and Indonesia's East Java have been reported only to contain limonoid derivatives. Biosynthetically, the pentacyclic triterpenes and limonoids are correlated with the tetracyclic triterpenes of the dammarane type [20]. Recently, we reported some tetracyclic triterpenes from the bark of the same plant [17]. These data suggest that the geographical sources of the plant, even on the same island of Java, can produce different types of secondary metabolites.

Preliminary biological activities of **1–6** were tested as inhibitors of eight receptor tyrosine kinases (RTKs), namely EGFR, HER2, HER4 (epidermal growth factor receptor), IGF1R, InsR (insulin receptor), KDR (kinase insert domain receptor), and PDGFRα and -β (platelet-derived growth factor receptor) [21]. The RTKs are enzymes involved in regulating cell growth and the development of cancer cells [22]. The biological assay was done according to the procedures previously reported [23]. Unfortunately, the results showed that the isolated compounds **1–6** were not active against these enzymes. Compounds **1–6** were also tested as inhibitors of β-lactamase, the enzyme in the bacteria that can degrade β-lactam antibiotic drugs [24]. Again, the results showed that no activities were found for **1–6** as the inhibitors of the enzyme.

In conclusion, six pentacyclic triterpenes (**1–6**) were isolated from the leaves of *S. koetjape* growing in West Java, Indonesia. Three of them are new and trivially named sandkoetjapics A–C (**1–3**), while **4–6** are the known triterpenes, namely katonic, bryonolic, and bryononic acids, respectively. This report is the first time that the pentacyclic triterpenes are isolated from the plant's leaves. Testing **1–6** as the inhibitors of eight RTKs and β-lactamase resulted in no activity for these compounds.

Experimental

General experimental procedures

Optical rotation was measured with an Autopol IV Rudolph Research Analytical. ^1H and ^{13}C NMR spectra were recorded

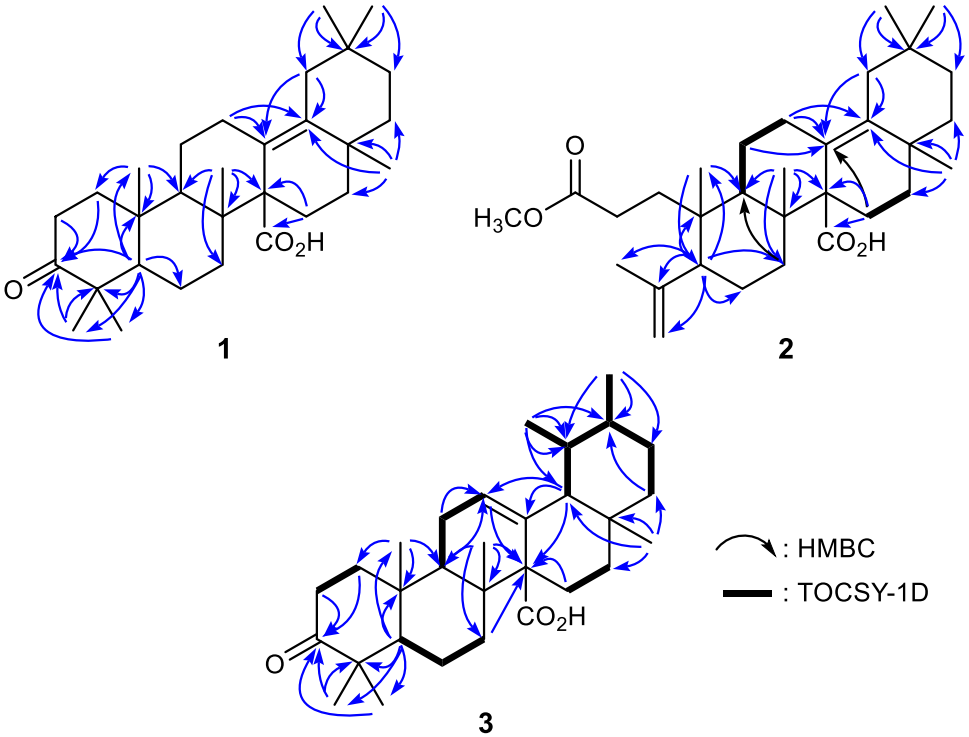

Fig. 2 Selected key HMBC correlations ($^{1}H \Rightarrow {}^{13}C$) found in compounds **1–3**

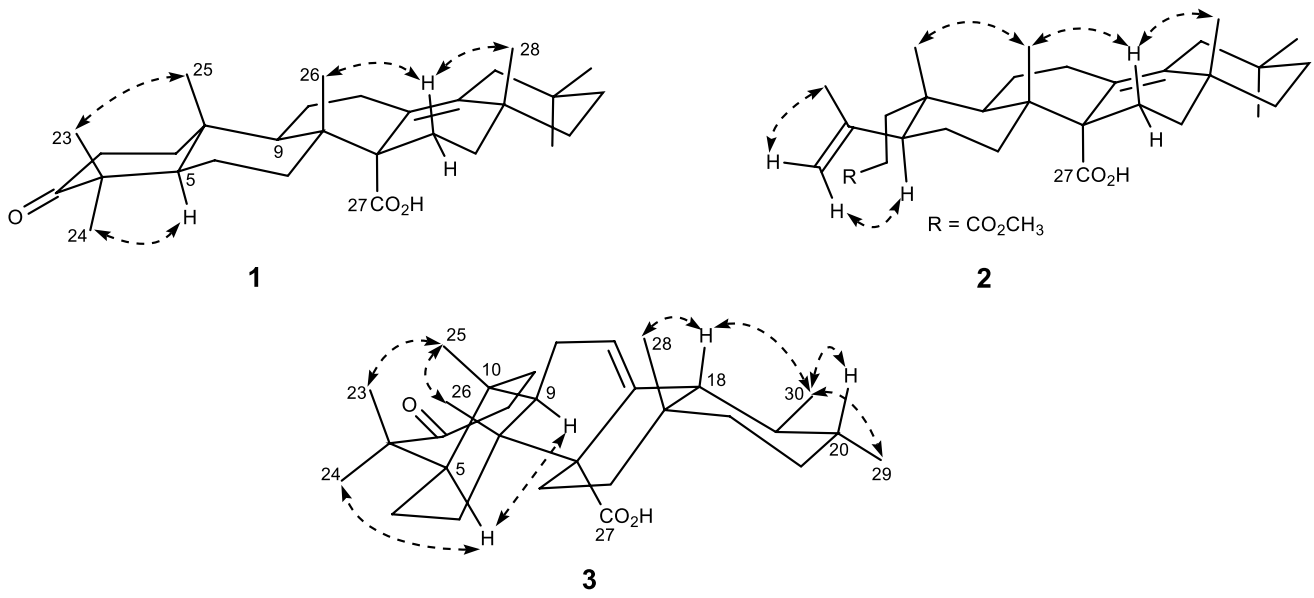

Fig. 3 Key NOE correlations found in compounds **1–3**

in $CDCl_3$ with a spectrometer of Agilent DD2 system operating at 500 (^{1}H) and 125 (^{13}C) MHz, using TMS as reference standards. HRMS spectra were obtained in either a negative or a positive mode using ESI-TOF Waters LCT Premier XE. Vacuum liquid chromatography (VLC) and centrifugal planar chromatography (CPC) were carried out using Merck Si gel 60 GF_{254} art. 7731 and 7749, respectively. Column chromatography (CC) was done using Si gel 40–60 mesh. Thin-layer chromatography (TLC) analysis used precoated Si gel plates (Merck Kieselgel 60 GF_{254}, 0.25 mm). Solvents (MeOH, acetone, EtOAc and *n*-hexane) for extraction, fractionation and purification were of technical grades, which were distilled before used. $CHCl_3$ and diisopropyl ether used in the purification were a pro analysis grade. The kits for kinase and β-lactamase assays were purchased from Promega and Abcam, respectively.

Plant material

The leaves of *S. koetjape* were collected in Pandeglang, Banten Province, Indonesia, in August 2013. The plant identity was determined by the staff of Herbarium Bandungense, Institut Teknologi Bandung, and the voucher specimen was deposited at the Herbarium (voucher number 11254).

Extraction and isolation

The dried and powdered leaves (1 kg) of *S. koetjape* were macerated in methanol at room temperature (3 × 24 h) which, after solvet evaporation, gave a gummy dark methanol extract (54 g). A part of the extract (20 g) was fractionated using VLC (silica gel 160 g) eluted with a gradient solvent system of *n*-hexane–EtOAc (each 200 mL) (9:1, 4x; 17:3, 2x; 4:1, 2x; 7:3, 3x; 3:2, 3x; 2:3, 2x; and 0:10, 2x) to give 18 fractions F1-F18. TLC analysis suggested that fractions F8-F14 contain terpenoid compounds. Fraction F8 (300 mg) was further fractionated (CPC; eluent: *n*-hexane-$CHCl_3$ = 9:1 to 2:3) yielding a subfraction (F14-7, 50 mg), which on purification (CC, *n*-hexane-disopropyl ether = 9:1 to 4:1) gave **2** (16 mg). The combined fractions F15 and F16 (F1516, 750 mg) were also fractionated by VLC and eluted by *n*-hexane–EtOAc = 19:1 and 15:5 to give 20 subfractions. The subfraction F1516-10 was then purified by CPC (gradient elution: *n*-hexane:diisopropyl ether from 4:1 to 100% diisopropyl ether) to give **3** (10 mg). The subfractions F1516-11-F1516-13 were combined (80 mg) and purified with CC (gradient elution: *n*-hexane:diisopropyl ether from 7:3 to 100% diisopropyl ether), yielded **2** (8 mg). Using the same methodology, from F17 gave **6** (23 mg), while F18 yielded **4** (11 mg) and **5** (49 mg).

Kinase and β-lactamase assays

The kinase assay was done according to the previously described procedures by us [23]. The tested compound was made in 5% DMSO and was diluted to a final concentration of 10 µM in kinase buffer and nuclease-free water. The assay used erlotinib as a positive control (10 µM). β-Lactamase assay was done according to the procedure published by Abcam using nitrocefin as the substrate [24]. The tested compound was also dissolved in 5% DMSO to a final concentration of 100 µM. The assay used tazobactam as a positive control (1 and 10 µM). The purity of **1–6** (> 95%) was determined by NMR.

Compound 1 (Sandkoetjapic acid A)

White powders. $[\alpha]^{20}_D = +10°$ (c 0.1, $CHCl_3$); UV (MeOH, λ_{max}) nm: 212 (log ε 3.98); IR (KBr, ν_{max}) cm^{-1}: 2954, 2924, 2858, 1721, 1685; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M\text{-}H]^-$ 453.3381 (calcd. for $C_{30}H_{45}O_3^-$: 453.3374).

Compound 2 (Sandkoetjapic acid B)

White powders. $[\alpha]^{20}_D = -33°$ (c 0.45, $CHCl_3$); UV (MeOH, λ_{max}) nm: 212 (log ε 4.05); IR (KBr, ν_{max}) cm^{-1}: 2949, 2924, 2864, 1739, 1686; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M + Na]^+$ 507.3436 (calcd. for $C_{31}H_{48}O_4Na^+$: 507.3445).

Compound 3 (Sandkoetjapic acid C)

White powders. $[\alpha]^{20}_D = +142°$ (c 0.1, $CHCl_3$); UV (MeOH, λ_{max}) nm: 213 (log ε 4.02); IR (KBr, ν_{max}) cm^{-1}: 3026, 2958, 2943, 2856, 1726, 1683; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M\text{-}H]^-$ 453.3360 (calcd. for $C_{30}H_{45}O_3^-$: 453.3374).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11418-022-01620-7.

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Pentacyclic triterpenes from the leaves extract of Sandoricum koetjape

by Leny Heliawati

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NOTE

Pentacyclic triterpenes from the leaves extract of *Sandoricum koetjape*

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Abstract
Three new pentacyclic triterpenes, trivially named sandkoetjapic acids A–C (**1**–**3**), have been isolated from the leaves extract of *Sandoricum koetjape*, along with the known triterpenes 3-oxo-olean-12-en-29-oic (**4**), bryonolic (**5**), and bryononic (**6**) acids. The structures of the new triterpenes were determined mainly by NMR spectroscopic and mass spectroscopic data. The isolation of these pentacyclic triterpenes in the plant's leaves is for the first time. Preliminary biological evaluation of **1**–**6** was done against eight receptor tyrosine kinases (RTKs), including EGFR, HER2, HER4 (epidermal growth factor receptor), IGF1R, InsR (insulin receptor), KDR (kinase insert domain receptor), and PDGFRα/-β (platelet-derived growth factor receptor), and their inhibitory properties against β-lactamase. The results showed that none of them were active both as the inhibitors of these RTKs and β-lactamase.

Keywords Sandkoetjapics A-C · Pentacyclic triterpenes · *Sandoricum koetjape* · Meliaceae · Receptor tyrosine kinases (RTKs) · β-lactamase

Introduction

Sandoricum koetjape Merr. (Meliaceae), locally known as "Kecapi" or "Sentul", produces edible fruits and is an economically significant tree of South Asia [1]. Its traditional uses are very limited. The local Indonesian people have reported the aqueous preparation of the bark as a tonic for women after childbirth. In addition, the same herbal preparation is also used for colic and leukorrhea treatments [2]. Phytochemical studies of this plant revealed the presence of terpenoid derivatives, including sesquiterpenes [3], triterpenes [2–8], and limonoids [9–13]. These studies showed that the leaves were the source of the limonoids, while the terpenoids were isolated from the woods and bark of the plant. Some of the compounds have been studied for their anti-inflammatory [14], antifeedant [9], cytotoxicity and anticancer agent [2, 3, 7, 10], DNA polymerase ß-inhibitors [15], and inhibitor of NO production [13].

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Recently, we reported the limonoid and triterpene constituents from the fruits and bark of *S. koetjape* grown in Indonesia [16, 17]. In a continuation of these studies, we now report the presence of three new pentacyclic triterpenes **1**–**3**, named sandkoetjapics A–C, from the plant's leaves, along with three known triterpenes **4**–**6**. Preliminary biological evaluation of **1**–**6** as inhibitors of receptor tyrosine kinases (RTKs) and β-lactamase is also described.

Results and discussion

Compound **1** (Fig. 1) was isolated as a white powder, $[\alpha]^{20}_{D} = +10°$. The UV spectrum showed an absorption maxima at 212 nm, indicating that **1** has no conjugated double bonds. The IR spectrum displayed absorptions for the carbonyl groups of ketone (ν_{max} 1721 cm^{-1}) and carboxylic acid (ν_{max} 1685 cm^{-1}). This compound exhibited a negative quasi-molecular ion in the HRESI-TOF spectrum at *m/z* 453.3381, consistent with the molecular formula $C_{30}H_{46}O_3$ (calcd. *m/z* for $C_{30}H_{45}O_3^-$ 453.3374) (DBE = 8). The NMR spectra (Tables 1 and 2) displayed seven methyl proton signals (δ_H 1.09, 1.03, 1.03, 0.96, 0.95, 0.93, 0.74), a ketone group (δ_C 218.1), and a carboxylic acid (δ_C 180.3) group. These mass and NMR data suggest that **1** is a pentacyclic triterpene in which one of the methyl groups is modified

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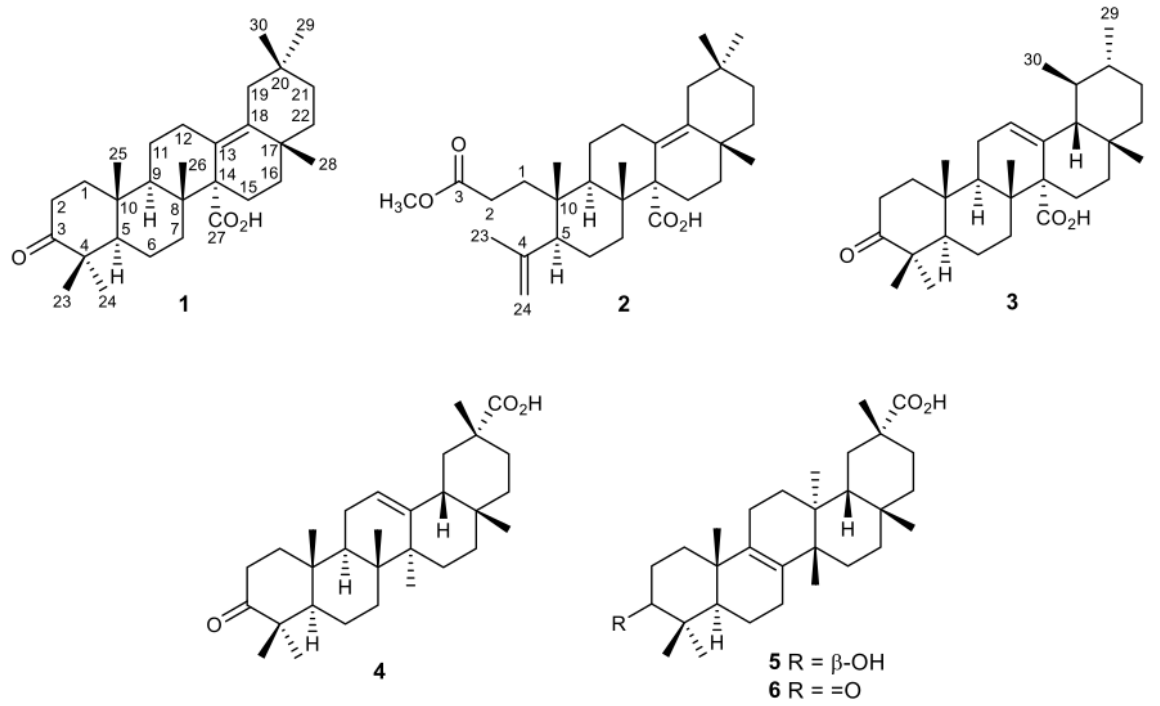

Fig. 1 Structures of pentacyclic triterpenes **1**–**6** from the leaves of *S. koetjape*

to a carboxylic acid group. The ^{13}C NMR spectrum also showed the presence of tetrasubstituted alkene signals (δ_C 138.0, 128.6), suggesting that **1** can be either multiflorane or olea-13(18)-en type. The presence of the HMBC correlations (Fig. 2) from the isolated methylene proton signals (δ_H 2.36, 1.71, H_2-19) to both the tetrasubstituted alkene carbon signals (δ_C 138.0, C-18; 128.6, C-13) is consistent with **1** as the olea-13(18)-en derivative. This was corroborated by the HMBC correlation between the C-18 signal and only one methyl signal (δ_H 1.03, H_3-28). No HMBC correlation was observed between any methyl proton signals and the C-13 signal, indicating that the carboxylic acid group is at C-27. Other HMBC correlations supporting structure **1** are shown in Fig. 2, and as expected, the C=O ketone group was placed at C-3. The stereochemistry of **1** was determined by the NOE correlations in the 2D-ROESY spectrum (Fig. 3). In aiding interpretation, the axial or equatorial position of the overlapping proton signals was predicted from the traces of the contour in the HSQC spectrum. The NOE correlations of H-5 and H_3-24, but not with H_3-23 and H_3-25, indicated that H-5 and H_3-25 are on the opposite side. Due to the very close of their chemical shift values, it is impossible to directly correlate the stereochemical relationship between H_3-25 and H_3-26. However, there were the NOE correlations for H_3-25/H-6_{ax} and H_3-26/H-15_{ax}/ H_3-28, indicating that H_3-26 and H_3-28 are on the same side of the olea-13(18)-en backbone, but on the opposite side from H-5 and H_3-24. Therefore, structure **1** was determined as 3-oxo-olean-13(18)-en-27-oic acid, trivially named sandkoetjapic acid A.

Compound **2**, trivially named as sandkoetjapic acid B, was also isolated as a white powder ($[\alpha]^{20}_D = -33°$) and has the molecular formula $C_{31}H_{48}O_4$ found $C_{31}H_{48}O_4Na^+$ at *m/z* 507.3436, calcd. 507.3445). The UV spectrum of **2** was similar to that of **1**, indicating also that this compound has no conjugated double bonds. The IR spectrum displayed absorptions for the carbonyl groups of ester (ν_{max} 1739 cm^{-1}) and carboxylic acid (ν_{max} 1686 cm^{-1}). The NMR data (Tables 1 and 2) showed signals for a 2-isopropenyl group (δ_H 4.86, 4.63, 1.72; δ_C 147.2, 113.7, 23.4), a methyl ester (δ_H 3.64; δ_C 174.7, 56.4), a carboxylic acid group (δ_C 181.3), a tetrasubstituted alkene (δ_C 138.1, 128.6), and five methyl groups (δ_H 1.02, 0.96, 0.94, 0.86, 0.74). These mass and spectroscopic data suggest that **2** is a 3,4-*seco* derivative of **1**, in which the carboxylic acid formed is further modified to a methyl ester. In the HMBC spectrum, long-range ^{1}H-^{13}C correlations were found from the signals of two methylenes H_2-19 and H_2-12 (δ_H 2.37, 1.72 and 2.82, 22.9) to the alkenic carbon signals (δ_C 138.1, C-18; 128.6, C-13). Furthermore, no methyl proton signal was found to have HMBC correlation with the C-13 signal, indicating that the position of the

Table 1 ^{1}H NMR data of compounds **1**–**3** in $CDCl_3$

C No	1	2	3	3**
1	1.94 (*m*); 1.47 (*m*)	1.68 (*m*); 1.60 (*m*)	1.94 (*ddd*, 13.3, 7.7, 4.3) 1.57 (*br dt*, 13.3, 8.7)	1.78 (*ddd*, 13.1, 7.8, 4.4) 1.47 (*br dt*, 13.1, 9.0)
2	2.46 (2H, *m*)	2.30 (*m*); 2.22 (*m*)	2.50 (*ddd*, 16.1, 8.7, 7.7) 2.44 (*ddd*, 16.1, 8.7, 4.3)	2.49 (*ddd*, 16.1, 9.0, 7.8) 2.38 (*ddd*, 16.1, 9.0, 4.4)
5	1.45 (*m*)	2.02 (*dd*, 10.6, 2.3)	1.36 (*m*)	1.45 (*m*)
6	1.51 (*m*); 1.39 (*m*)	1.69 (*m*); 1.42 (*m*)	1.44 (2H, *m*)	1.35 (2H, *m*)
7	2.19 (*m*); 1.65 (*m*)	2.04 (*td*, 13.5, 3.2) 1.61 (*m*)	1.76 (*m*); 1.16 (*m*)	1.85 (*m*); 1.64 (*m*)
9	1.51 (*m*)	1.67 (*dd*, 12.9, 9.4)*	2.33 (*dd*, 11.2, 5.6)	2.79 (*dd*, 11.5, 5.2)
11	1.51 (*m*); 1.39 (*m*)	1.49 (*m*) 1.34 (*qd*, 12.9, 6.0)*	2.02 (*m*); 2.00 (*m*)	2.06 (*m*); 1.99 (*m*)
12	2.83 (*dd*, 15.0, 5.0) 2.28 (*m*)	2.82 (*dd*, 14.5, 4.2)* 2.29 (*ddd*, 14.5, 12.9, 5.3)*	5.59 (*br dd*, 4.6, 2.5)	5.69 (*br dd*, 5.0, 2.5)
15	1.94 (*m*); 1.75 (*m*)	1.97 (*dt*, 13.5, 3.2) 1.71 (*dd*, 13.5, 9.2)*	1.98 (*br d*, 13.6) 1.78 (*td*, 13.6, 4.3)	2.37 (*m*); 1.88 (*m*)
16	1.41 (*m*); 1.35 (*m*)	1.41 (*m*); 1.38 (*m*)	2.11 (*td*, 13.4, 3.6) 0.91 (*br d*, 13.4)	2.46 (*m*); 1.02 (*m*)
18	–	–	1.37 (*m*)	1.46 (*d*, 11.5)
19	2.36 (*br dd*, 13.8, 1.5) 1.71 (*br d*, 13.8)	2.37 (*br d*, 13.7) 1.72 (*br d*, 13.7)*	0.89 (*m*)	1.29 (*m*)
20	–	–	0.87 (*m*)	0.87 (*m*)
21	1.50 (*m*); 1.16 (*m*)	1.49 (*m*) 1.15 (*dm*, 12.8)	1.34 (*m*); 1.25 (*m*)	1.29 (2H, *m*)
22	1.34 (2H, *m*)	1.34 (2H, *m*)	1.42 (*m*); 1.25 (*m*)	1.44 (*m*); 1.29 (*m*)
23	1.03 (*s*)	1.72 (*s*)	1.03 (*s*)	1.02 (*s*)
24	1.09 (*s*)	4.86 (*br s*); 4.63 (*br s*)	1.06 (*s*)	0.95 (*s*)
25	0.95 (*s*)	0.86 (*s*)	1.05 (*s*)	0.98 (*s*)
26	0.93 (*s*)	0.94 (*s*)	1.07 (*s*)	1.10 (*s*)
28	1.03 (*s*)	1.02 (*s*)	0.84 (*s*)	0.97 (*s*)
29	0.74 (*s*)	0.73 (*s*)	0.79 (*br d*, 5.5)	0.78 (*d*, 6.3)
30	0.96 (*s*)	0.96 (*s*)	0.86 (*br s*)	1.10 (*d*, 6.0)
OCH_3	–	3.64 (*s*)	–	–

*Obtained from TOCSY-1D spectra

**Measured in pyridine-d_6

carboxylic acid group is also at C-27 as in **1**. As expected, the HMBC correlations also confirmed the attachments of the 2-isopropenyl group at C-5 and the ester propanoyl at C-10, as shown in Fig. 2. Some of the coupling constants of the overlapping proton signals were determined by analysis of its 1D-TOCSY spectra, which can identify the axial arientation of H-5, H-9, and H-15. In the 1D-ROESY spectra, the NOE correlations were found for H_3-25/H_3-26/H-15_{ax}/H_3-28. No NOE correlation was found between H-5 and H_3-25, but between H-5 and one of the methylenic alkene signal. These NOE correlations are consistent with **2** having the original structure of olean-13(18)-en. Therefore, structure **2** is determined to sandkoetjapic acid B. However, the presence of the methyl ester group in **2** might be an artifact due to the use of methanol in the extraction process.

Compound **3**, isolated as a white powder ($[\alpha]^{20}_D = +142°$), has the same molecular formula as **1** (*m/z* for $[M\text{-}H]^-$ 453.3360, calcd. for $C_{30}H_{45}O_3^-$ 453.3374). The UV and IR absorptions were also similar to those of **1**, indicating that **3** is an isomer of **1**. However, the IR spectrum also showed the absorption at ν_{max} 3026 cm^{-1}, suggesting the presence of a trisubstituted alkene group. The NMR data of **3** also resembled those of **1**, except that in **3** a trisubstituted alkenyl proton signal at δ_H 5.59 (Table 1) was observed. In addition, two methyl proton signals in **3** appeared as a doublet (δ_H 0.79) and a broad singlet (δ_H 0.86) in $CDCl_3$ or as a pair of doublets (δ_H 1.10, 0.78) in pyridne-d_5 (Table 1). Moreover, **3** has less than one quarternary aliphatic carbon, which is replaced by two methine groups (δ_H 0.89, 0.87; δ_C 39.6, 37.7). These mass and NMR spectroscopic data are consistent with **3** having a structure

Table 2 ^{13}C NMR data of compounds **1–3** in $CDCl_3$

C No	1	2	3	3*
1	39.3	33.9	39.3	39.8
2	34.1	28.4	34.0	34.5
3	218.1	174.7	218.0	217.0
4	47.2	147.2	47.1	47.4
5	54.1	49.7	54.6	55.1
6	21.3	24.6	19.7	20.2
7	34.9	34.5	36.0	36.8
8	41.6	41.3	39.8	40.1
9	51.5	42.2	45.9	46.5
10	37.1	39.8	36.6	37.1
11	21.3	21.3	22.9	23.7
12	26.5	26.5	128.4	128.1
13	128.6	128.6	133.2	135.1
14	59.2	59.3	55.8	56.8
15	23.5	23.2	22.4	23.3
16	37.0	37.1	28.9	29.9
17	34.7	34.7	33.7	34.3
18	138.0	138.1	60.3	61.0
19	38.9	38.9	37.7	38.2
20	34.2	34.2	39.6	40.0
21	35.3	35.4	30.3	31.0
22	39.2	39.2	40.8	41.6
23	21.2	23.4	21.3	21.7
24	27.0	113.7	27.0	27.1
25	16.3	20.3	16.4	16.6
26	18.4	18.7	18.1	18.6
27	180.3	181.1	180.9	178.0
28	23.9	24.0	29.0	29.7
29	24.0	23.9	17.8	21.7
30	24.0	32.4	21.4	18.8
OCH_3	–	51.6	–	–

*Measured in pyridine-d_6

of urs-12-en. In the HMBC spectrum, it was found that no methyl proton signal was correlated with the quarternary carbon signal of the trisubstituted alkene, indicating that the carboxylic acid group is also at C-27. As expected, the HMBC correlations also allowed the ketone group to be placed at C-3. Thus, **3** has the basic structure of 3-oxo-urs-12-en-27-oic acid. Other HMBC correlations supporting structure **3** are shown in Fig. 2. 1D-TOCSY measurements are also used to determine some ^1H-^1H coupling constants. The stereochemistry of **3** was determined by both 1D- and 2D-ROESY spectra measured in pyridine-d_5. These spectra clearly observed the presence of NOE enhancements for H_3-24/H-5/H-9 on one side and H_3-23/H_3-25/H_3-26 on the other side (Fig. 3). The same NOE enhancements were also observed for H_3-28/H-18/H_3-30/H_3-29. Furthermore, irradiation at δ_H 1.10 (H_3-26 and H_3-30) increased the signal intensities of H-15$_{ax}$, H-20, H_3-28, and H_3-29, confirming the stereochemical relationship between H_3-26 and H_3-28, and the axial orientation of H-20. These stereochemical assignments confirmed the structure **3** as 3-oxo-urs-12-en-27-oic acid, trivially named sandkoetjapic acid C. A literature search showed that **3** had been reported as the chemical transformation product of plectranthoic acid B [18].

The other three isolated compounds **4–6** were the known pentacyclic triterpenes and were determined as 3-oxo-olean-12-en-29-oic, bryonolic, and bryononic acids [5, 19], respectively, based on mass and NMR spectroscopic data.

This paper reports for the first time the presence of pentacyclic triterpenes in the leaves of *S. koetjape* growing in West Java, Indonesia. The leaves of *S. koetjape* collected in Malaysia, Thailand, and Indonesia's East Java have been reported only to contain limonoid derivatives. Biosynthetically, the pentacyclic triterpenes and limonoids are correlated with the tetracyclic triterpenes of the dammarane type [20]. Recently, we reported some tetracyclic triterpenes from the bark of the same plant [17]. These data suggest that the geographical sources of the plant, even on the same island of Java, can produce different types of secondary metabolites.

Preliminary biological activities of **1–6** were tested as inhibitors of eight receptor tyrosine kinases (RTKs), namely EGFR, HER2, HER4 (epidermal growth factor receptor), IGF1R, InsR (insulin receptor), KDR (kinase insert domain receptor), and PDGFRα and -β (platelet-derived growth factor receptor) [21]. The RTKs are enzymes involved in regulating cell growth and the development of cancer cells [22]. The biological assay was done according to the procedures previously reported [23]. Unfortunately, the results showed that the isolated compounds **1–6** were not active against these enzymes. Compounds **1–6** were also tested as inhibitors of β-lactamase, the enzyme in the bacteria that can degrade β-lactam antibiotic drugs [24]. Again, the results showed that no activities were found for **1–6** as the inhibitors of the enzyme.

In conclusion, six pentacyclic triterpenes (**1–6**) were isolated from the leaves of *S. koetjape* growing in West Java, Indonesia. Three of them are new and trivially named sandkoetjapics A–C (**1–3**), while **4–6** are the known triterpenes, namely katonic, bryonolic, and bryononic acids, respectively. This report is the first time that the pentacyclic triterpenes are isolated from the plant's leaves. Testing **1–6** as the inhibitors of eight RTKs and β-lactamase resulted in no activity for these compounds.

Experimental

General experimental procedures

Optical rotation was measured with an Autopol IV Rudolph Research Analytical. ^1H and ^{13}C NMR spectra were recorded

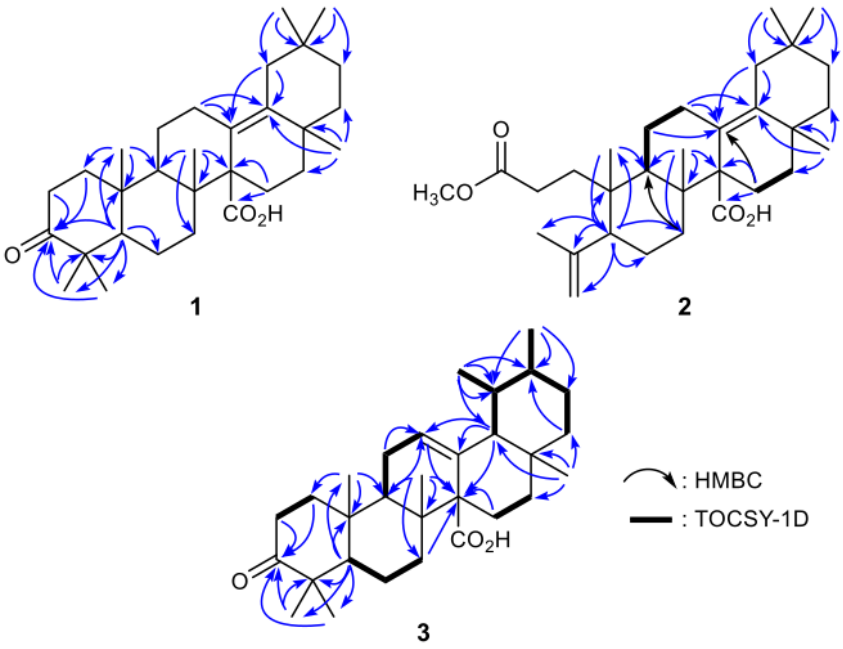

Fig. 2 Selected key HMBC correlations ($^{1}H \Rightarrow {}^{13}C$) found in compounds **1–3**

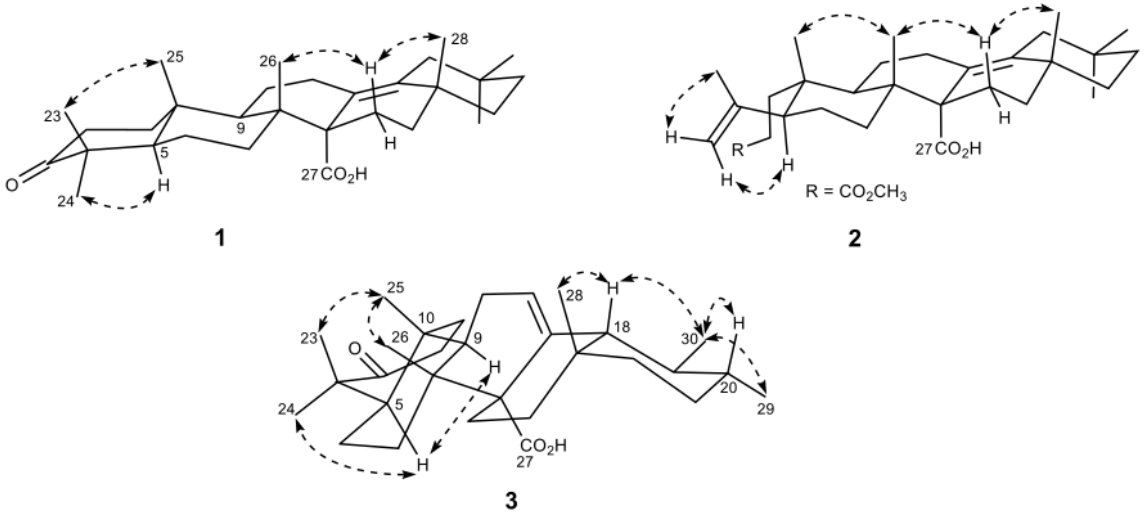

Fig. 3 Key NOE correlations found in compounds **1–3**

in $CDCl_3$ with a spectrometer of Agilent DD2 system operating at 500 (^{1}H) and 125 (^{13}C) MHz, using TMS as reference standards. HRMS spectra were obtained in either a negative or a positive mode using ESI-TOF Waters LCT Premier XE. Vacuum liquid chromatography (VLC) and centrifugal planar chromatography (CPC) were carried out using Merck Si gel 60 GF_{254} art. 7731 and 7749, respectively. Column chromatography (CC) was done using Si gel 40–60 mesh.

Thin-layer chromatography (TLC) analysis used precoated Si gel plates (Merck Kieselgel 60 GF_{254}, 0.25 mm). Solvents (MeOH, acetone, EtOAc and *n*-hexane) for extraction, fractionation and purification were of technical grades, which were distilled before used. $CHCl_3$ and diisopropyl ether used in the purification were a pro analysis grade. The kits for kinase and β-lactamase assays were purchased from Promega and Abcam, respectively.

Plant material

The leaves of *S. koetjape* were collected in Pandeglang, Banten Province, Indonesia, in August 2013. The plant identity was determined by the staff of Herbarium Bandungense, Institut Teknologi Bandung, and the voucher specimen was deposited at the Herbarium (voucher number 11254).

Extraction and isolation

The dried and powdered leaves (1 kg) of *S. koetjape* were macerated in methanol at room temperature (3×24 h) which, after solvet evaporation, gave a gummy dark methanol extract (54 g). A part of the extract (20 g) was fractionated using VLC (silica gel 160 g) eluted with a gradient solvent system of *n*-hexane–EtOAc (each 200 mL) (9:1, 4x; 17:3, 2x; 4:1, 2x; 7:3, 3x; 3:2, 3x; 2:3, 2x; and 0:10, 2x) to give 18 fractions F1-F18. TLC analysis suggested that fractions F8-F14 contain terpenoid compounds. Fraction F8 (300 mg) was further fractionated (CPC; eluent: *n*-hexane-$CHCl_3$=9:1 to 2:3) yielding a subfraction (F14-7, 50 mg), which on purification (CC, *n*-hexane-disopropyl ether=9:1 to 4:1) gave **2** (16 mg). The combined fractions F15 and F16 (F1516, 750 mg) were also fractionated by VLC and eluted by *n*-hexane–EtOAc=19:1 and 15:5 to give 20 subfractions. The subfraction F1516-10 was then purified by CPC (gradient elution: *n*-hexane:diisopropyl ether from 4:1 to 100% diisopropyl ether) to give **3** (10 mg). The subfractions F1516-11-F1516-13 were combined (80 mg) and purified with CC (gradient elution: *n*-hexane:diisopropyl ether from 7:3 to 100% diisopropyl ether), yielded **2** (8 mg). Using the same methodology, from F17 gave **6** (23 mg), while F18 yielded **4** (11 mg) and **5** (49 mg).

Kinase and β-lactamase assays

The kinase assay was done according to the previously described procedures by us [23]. The tested compound was made in 5% DMSO and was diluted to a final concentration of 10 µM in kinase buffer and nuclease-free water. The assay used erlotinib as a positive control (10 µM). β-Lactamase assay was done according to the procedure published by Abcam using nitrocefin as the substrate [24]. The tested compound was also dissolved in 5% DMSO to a final concentration of 100 µM. The assay used tazobactam as a positive control (1 and 10 µM). The purity of **1–6** (> 95%) was determined by NMR.

Compound 1 (Sandkoetjapic acid A)

White powders. $[\alpha]^{20}_D = +10°$ (c 0.1, $CHCl_3$); UV (MeOH, λ_{max}) nm: 212 (log ε 3.98); IR (KBr, ν_{max}) cm^{-1}: 2954, 2924, 2858, 1721, 1685; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M-H]^-$ 453.3381 (calcd. for $C_{30}H_{45}O_3^-$: 453.3374).

Compound 2 (Sandkoetjapic acid B)

White powders. $[\alpha]^{20}_D = -33°$ (c 0.45, $CHCl_3$); UV (MeOH, λ_{max}) nm: 212 (log ε 4.05); IR (KBr, ν_{max}) cm^{-1}: 2949, 2924, 2864, 1739, 1686; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M+Na]^+$ 507.3436 (calcd. for $C_{31}H_{48}O_4Na^+$: 507.3445).

Compound 3 (Sandkoetjapic acid C)

White powders. $[\alpha]^{20}_D = +142°$ (c 0.1, $CHCl_3$); UV (MeOH, λ_{max}) nm: 213 (log ε 4.02); IR (KBr, ν_{max}) cm^{-1}: 3026, 2958, 2943, 2856, 1726, 1683; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$), see Table 2; HRESI-TOF-MS *m/z*: $[M-H]^-$ 453.3360 (calcd. for $C_{30}H_{45}O_3^-$: 453.3374).

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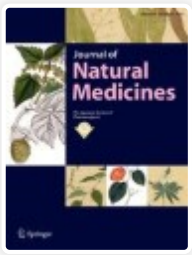

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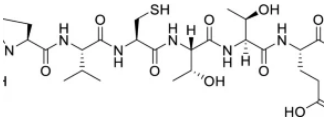

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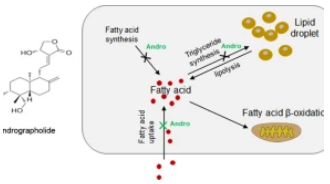

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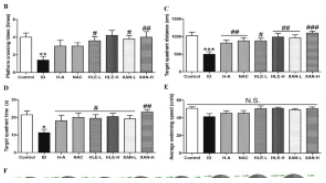

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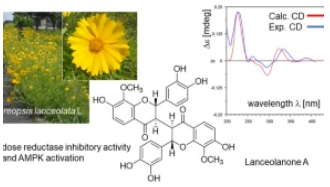

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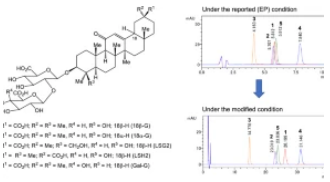

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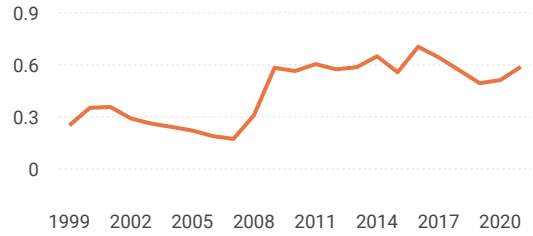

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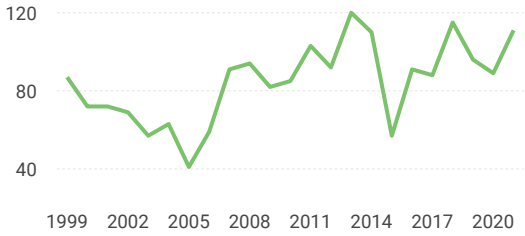

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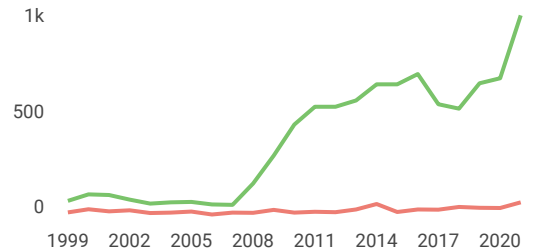

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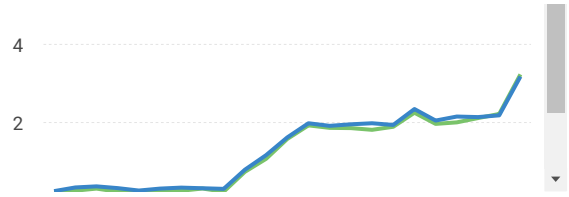

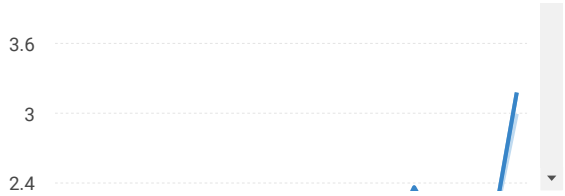

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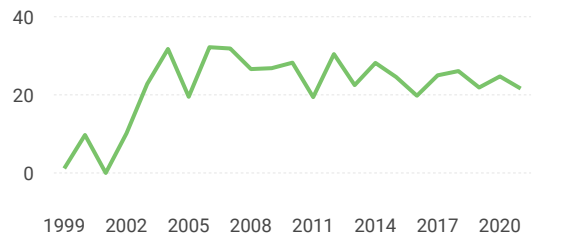

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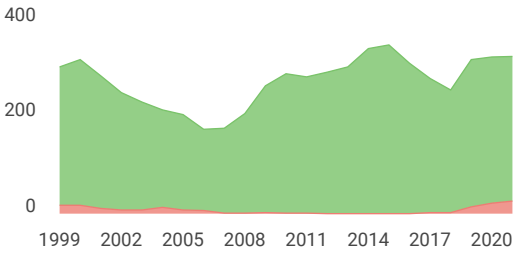

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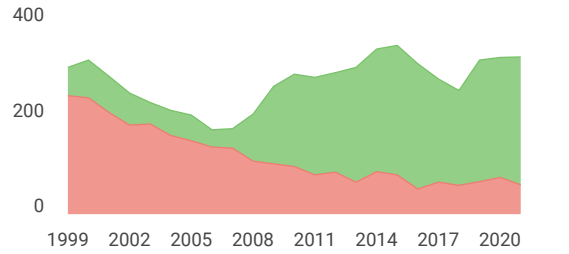

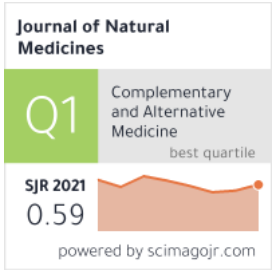

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