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been fractionated based on polarity to become hexane, ethyl acetate, butanol, and aqueous fractions. All the fractions stimulated their alkaline phosphatase (ALP) activity to 138.11 ± 9.72%, 108 ± 5.05%, 148.56 ± 8.47, and 144.58 ± 1.04, respectively. Conclusions The extract and fractions of E. serratus L. can successfully inhibit DPPH radical scavenging value and increase ALP activities as markers of osteoblast functions.

June 25, 2021

In vitro antimalarial activity of _Garcinia parvifolia_ Miq. Stem extracts and fractions on _Plasmodium falciparum_ lactate dehydrogenase (LDH) assay

Marsih Wijayanti, Hilkatul Ilmi, Einstenia Kemalahayati, Lidya Tumewu, Fendi Yoga Wardana, Suciati, Achmad Fuad Hafid, Aty Widyawaruyanti

Page range: 839-844

Abstract

Objectives The rapid spread of antimalarial drug resistance is becoming a problem in the treatment of malaria. The fact was indicated the importance of finding new antimalarial drugs. The genus Garcinia is well known to be a rich source of bioactive prenylated xanthones and triterpenes reported for their antimalarial activity. Garcinia parvifolia is one of the Garcinia genera that can be explored for the search of new antimalarial drugs. This study was aimed to determine the antimalarial activities of G. parvifolia extracts and fractions. Methods Garcinia parvifolia Miq. stem was collected from Balikpapan Botanical Garden in East Kalimantan, Indonesia, was extracted gradually with n-hexane, dichloromethane, and methanol by ultrasonic assisted method. The most active extract was further separated using the open column chromatography method. All extracts and fractions were tested against Plasmodium falciparum 3D7 using lactate dehydrogenase (LDH) assay and followed by IC 50 determination. Results The results showed that all extracts inhibit P. falciparum growth by LDH assay. The highest inhibition was showed by dichloromethane stem extract (BP12-S-D) with the IC 50 value of 6.61 ± 0.09 µg/mL. Further fractionation of BP12-S-D has obtained 10 fractions. All of them were identified by TLC, and a brownish-yellow spot (fraction-1) appears after spraying with 10% H 2 SO 4 . Fraction-1 (F1) performed the highest parasite growth inhibition with the IC 50 value of 6.00 ± 0.03 µg/mL compared with other fractions. This fraction was classified as having a promising activity of antimalarial. The fraction-1 was identified using HPLC, and two major peaks were observed (A and B). The UV–Vis spectra showed the absorption at wavelengths 250 and 278 (A), 243, 281, and

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In vitro antimalarial activity of *Garcinia parvifolia* Miq. Stem extracts and fractions on *Plasmodium falciparum* lactate dehydrogenase (LDH) assay

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Abstract

Objectives: The rapid spread of antimalarial drug resistance is becoming a problem in the treatment of malaria. The fact was indicated the importance of finding new antimalarial drugs. The genus Garcinia is well known to be a rich source of bioactive prenylated xanthones and triterpenes reported for their antimalarial activity. *Garcinia parvifolia* is one of the Garcinia genera that can be explored for the search of new antimalarial drugs. This study was aimed to determine the antimalarial activities of *G. parvifolia* extracts and fractions.

Methods: *Garcinia parvifolia* Miq. stem was collected from Balikpapan Botanical Garden in East Kalimantan, Indonesia, was extracted gradually with n-hexane, dichloromethane, and methanol by ultrasonic assisted method. The most active extract was further separated using the open column chromatography method. All extracts and fractions were tested against *Plasmodium falciparum* 3D7 using lactate dehydrogenase (LDH) assay and followed by IC_{50} determination.

Results: The results showed that all extracts inhibit *P. falciparum* growth by LDH assay. The highest inhibition was showed by dichloromethane stem extract (BP12-S-D) with the IC_{50} value of 6.61 ± 0.09 μg/mL. Further fractionation of BP12-S-D has obtained 10 fractions. All of them were identified by TLC, and a brownish-yellow spot (fraction-1) appears after spraying with 10% H_2SO_4. Fraction-1 (F1) performed the highest parasite growth inhibition with the IC_{50} value of 6.00 ± 0.03 μg/mL compared with other fractions. This fraction was classified as having a promising activity of antimalarial. The fraction-1 was identified using HPLC, and two major peaks were observed (A and B). The UV–Vis spectra showed the absorption at wavelengths 250 and 278 (A), 243, 281, and 317 nm (B). Based on the profile of TLC, HPLC, and UV–Vis spectra of F1, it was expected that the active compounds are flavonoid (A) and xanthone (B).

Conclusions: The fraction-1 of dichloromethane extract of *G. parvifolia* Miq. stem has the highest antimalarial activity. It might be a potential candidate for the new antimalarial drug.

Keywords: antimalarial activity; *Garcinia parvifolia* Miq.; lactate dehydrogenase (LDH).

Introduction

Malaria is a type of infectious disease that mainly occurs in tropical and subtropical regions, and it remains a problem in the world [1–3]. The World Health Organization (WHO) reported that malaria cases in 2018 are estimated to be 228 million (7.9 million or 3.4% of cases in Southeast Asia). Each year, more than 405,000 people die of malaria, particularly children under the age of five and pregnant women [4]. The appearance of drug-resistant *Plasmodium falciparum* since 1960 has made the treatment of malaria increasingly problematic [5–7]. Therefore, discovering new antimalarial drugs is a priority in the health sector [8]. Recently, attention was focused on medicinal plants to provide new antimalarial drugs [9].

Clusiaceae family has 40 genus and more than 1,000 species spread in tropic and subtropic areas [10]. The main genus in the Clusiaceae is Garcinia and Calophyllum [11].

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Clusiaceae are widely spread in Asia, Africa, New Caledonia, and Polynesia [12]. *Garcinia parvifolia* Miq., one species of the Clusiaceae family, is native in tropical, and subtropical countries of South East Asia such as Malaysia, Thailand, Brunei, and Indonesia [13, 14]. This plant is known as *Garcinia dioica* Blume and *Garcinia globulosa* Ridley. The common name for it is Cherry mangosteen, Kandis, and yellow Kandis [15].

Garcinia parvifolia has various biological actions, such as antioxidants [13], antimicrobials [7, 11, 16–18], antiplatelet [19], antiplasmodial [7, 17, 20–22], and larvicide [23]. The fruit and young leaf are sometimes eaten as a vegetable [10]. The *n*-hexane extract of stem bark of *G. parvifolia* Miq. inhibited malarial parasite growth against *P. falciparum* FCR3 (chloroquine-resistance strain) with the IC_{50} value of 4.11 μg/mL [7]. The n-hexane fraction of *G. parvifolia* Miq. stem bark showed antimalarial activity against *Plasmodium berghei* with an ED_{50} value of 74.54 ± 10 mg/kg body weight [21]. Several compounds have been isolated from this plant and whereas identified as flavonoids, triterpenoids, steroids, and xanthones (rubraxanthone, cowinin, and the novel cytotoxic griffiparvixanthone) [11, 24, 25]. Based on these previous studies, *G. parvifolia* is potential as a source of antimalarial drugs. Research on the stems of *G. parvifolia* has not been reported. Therefore, this study was aimed to determine the antimalarial activities of *G. parvifolia* stem extracts and fractions.

Materials and methods

Plant material

The stems of *G. parvifolia* were collected from Balikpapan Botanical Garden, East Kalimantan, Indonesia. Identification by a licensed botanist at Purwodadi Botanical Garden, East Java, Indonesia. A voucher specimen number is B-109/IPH.06/AP.01/II/2020. Raw material has been stored at the herbarium of the Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.

Extraction and fractionation

The stem of *G. parvifolia* Miq. was extracted gradually with n-hexane, dichloromethane, and methanol by ultrasound-assisted extraction. The most active extract was further separated using open column chromatography with a gradient of chloroform and methanol (100–0%). Based on thin layer chromatography (TLC) profiles, several fractions with the same profile were combined. All extracts and fractions were identified by TLC profiles using standard methods [26]. All samples were diluted in methanol. TLC was performed using chloroform: methanol (98: 2) as the mobile phase and silica gel 60 F_{254} as the stationary phase. Furthermore, the plates were visualized directly after drying and with the help of UV at 254 and 366 nm in UV TLC visualizer. Ten percent H_2SO_4 is used as a spray reagent. Extracts and fractions were tested against *P. falciparum* 3D7 using lactate dehydrogenase (LDH) assay and followed by IC_{50} determination.

Subsequently, the active fraction profile was analyzed using TLC and high-performance liquid chromatography (HPLC) methods. Analytical HPLC system was run on a Shimadzu, LC-06 included two LC-10AD pumps and SCL-10A controller with analytical column Merck RP-18 (4.6 × 250 mm × 5 μm). Fractions were eluted in acetonitrile: water (7:3 v/v) mixture at a flow rate of 0.5 mL/min and injection volume of 40 μL.

Cultivation of *Plasmodium falciparum*

Plasmodium falciparum strain 3D7 (chloroquine-sensitive strain) was obtained from the Center for Natural Product Medicine Research and Development (C-NPMRD), Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia. The culture was established using the method by Trager and Jensen with some modifications [27]. Parasites were maintained in fresh human erythrocytes (type O red blood cell) at 2% hematocrit in RPMI 1640 medium (Gibco) containing 10% v/v AlbuMAX™ II (Gibco); 0.05 g hypoxanthine (Sigma); 2 g sodium bicarbonate, and 0.5 mL gentamycin (Sigma). Human RBCs were received from the Indonesian Red Cross, Surabaya, Indonesia.

In vitro antimalarial assay

In vitro assay of antimalarial activity was carried out by LDH assay [28, 29]. The lactate dehydrogenase (LDH) method was performed using a 96-well plate (flat bottom). Synchronized ring-stage parasites were obtained by 5% w/v sorbitol [30]. Briefly, the continuous culture of the parasites was maintained in a complete medium. Extracts and fractions of *G. parvifolia* Miq. stem was screened at a concentration 10 μg/mL. One microliter of the sample was added to each well and repeated three times. Then added 99 μL pf parasites (ring-stage). Furthermore, the assay plate was incubated at 37 °C in a gas mixture consisting of 5% O_2, 5% CO_2, and 90% N_2 for 72 h. After 72 h of incubation, the well plate was kept at −30 °C overnight. The antimalarial activity was measured by an LDH assay. Ten milliliters of LDH-buffer (Tris-HCl, sodium L-lactate, Triton X-100, deionized water) was added 2 mg NBT (10 mg/mL, Sigma), 50 μL APAD stock (10 mg/mL, Oriental Yeast Co., Ltd.), 200 μL Diaphorase stock (50 units/mL, Sigma). Mix gently and keep the substrate in the dark. Add 90 μL substrate per well plate. Cover with aluminum foil and place on a flatbed shaker at 400 rpm at room temperature. Incubate for 30 min. The absorbance of each well measured at wavelength 650 nm using a multiscan sky high microplate spectrophotometer (Thermo fisher scientific). The inhibition rate was calculated with the absorbance of uninfected wells defined as 100% inhibition. Hit sample was defined as those inhibiting more than 50% activity at 10 μg/mL. The IC_{50} of the hit sample was determined under the same assay condition for the screening with the addition of sample in serial dilution (0.01; 0.05; 0.1; 0.5; 1; 5; 10 and 50 μg/mL). The IC_{50} values were calculated using GraphPad Prism version 7.0 software.

Results

The stem of *G. parvifolia* Miq. was extracted gradually using *n*-hexane (BP12-S-H), dichloromethane (BP12-S-D), and methanol (BP12-S-M). This extraction obtained BP12-S-H (1.73 g), BP12-S-D (10.08 g), and BP12-S-M (15.35 g). The antimalarial activity showed that only BP12-S-D inhibited *P. falciparum* growth with the IC_{50} value of 6.61 ± 0.09 µg/mL (Table 1). Quality control parameters, including Z′-factor, S/B, S/N, and CV (%), were also calculated with values of 0.84, 7.42, 266.40, and 22.47 indicating the high quality and performance of the screening.

Future fractionation of BP12-S-D (active extract) by open column chromatography and obtained 10 fractions (F1–F10). Screening antimalarial activity showed that seven fractions had inhibitions against *P. falciparum* 3D7 more than 50% at 10 µg/mL (Figure 1). Therefore, the IC_{50} calculation is carried out on these fractions. The result showed that fraction-1 (F1) had the most active fraction with an IC_{50} value of 6.00 ± 0.03 µg/mL (Table 2). This fraction was classified as active antimalarial based on Chinchilla et al. [31]. The TLC profile shows a dominant brownish-yellow spot at the white light after sprayed with H_2SO_4 10% and heated at 105 °C for 5 min. These spots indicate that a compound is a xanthone group (Figure 2).

Table 1: Antimalarial activity (IC_{50}) from extracts of *G. parvifolia* stem.

Sample	IC_{50}, µg/mL
BP12-S-H	NA
BP12-S-D	6.61 ± 0.09
BP12-S-M	NA

NA, Not active; Data are reported as mean ± SD from three independent experiments.

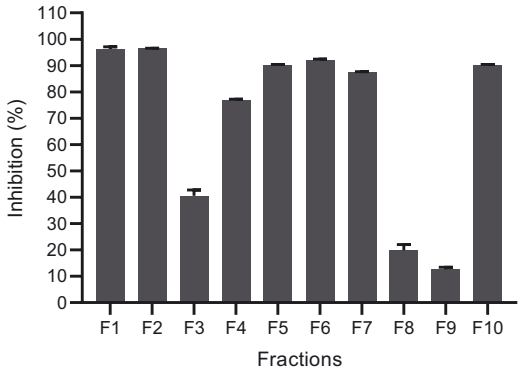

Figure 1: Inhibition percentages of all fractions against *P. falciparum* 3D7 at a concentration of 10 µg/mL. Data are reported as mean ± SD from three independent experiments.

Table 2: Antimalarial activity (IC_{50}) of seven fractions from a dichloromethane extract of *G. parvifolia* stem (BP12-S-D).

Sample	IC_{50}, µg/mL
F1	6.00 ± 0.03
F2	7.14 ± 0.03
F4	7.51 ± 0.01
F5	6.72 ± 0.02
F6	7.49 ± 0.03
F7	7.72 ± 0.03
F10	7.58 ± 0.03

Data are reported as mean ± SD from three independent experiments.

HPLC profile of F1 showed that two major peaks at minute retention times 22.580 (A) and 26.659 (B) (Figure 3). Peak A in The UV–Vis spectra has maximum absorption at 250 and 278 nm (Figure 4). Meanwhile, peak B has maximum absorption 243, 281, and 317 nm (Figure 5).

Discussion

Medicinal plants are good resources to found a new antimalarial drug candidate. In the present study, we examined the possible antimalarial activity of *G. parvifolia* Miq. extracts and fractions. *G. parvifolia*, which belongs to the family of Clusiaceae, is widely distributed in tropical and subtropical countries of South East Asia such as Malaysia, Brunei, Thailand, and Indonesia [13, 14]. This plant is known to have many pharmacological effects. Infusion is drunk as a post-partum medication by people in Riau Province, Sumatra, Indonesia [32]. This tree's fruit is edible, and the young leaves are sometimes eaten as a vegetable [14].

In this study, *G. parvifolia* stem was subjected to extraction in different polarities of solvents, and antimalarial activities of the extracts were examined against *P. falciparum* 3D7. The results revealed that BP12-S-D possessed the most potent activity with the IC_{50} values of 6.61 ± 0.09 µg/mL (Table 1). We further fractionated the BP12-S-D to obtained 10 fractions (F1–F10). The antimalarial activity showed that fraction 1 (F1) is the most active fraction with the IC_{50} values of 6.00 ± 0.03 µg/mL (Table 2). Based on the antimalarial criteria of Chincilla et al. (2012), BP12-S-D and F1 were classified as active as antimalarials. Basic criteria for antiparasitic drug discovery activities of extracts were classified into four classes according to their IC_{50}. Very active (<5 µg/mL), active (>5–50 µg/mL), weakly active (>50–100 µg/mL), and inactive (>100 µg/mL) [31].

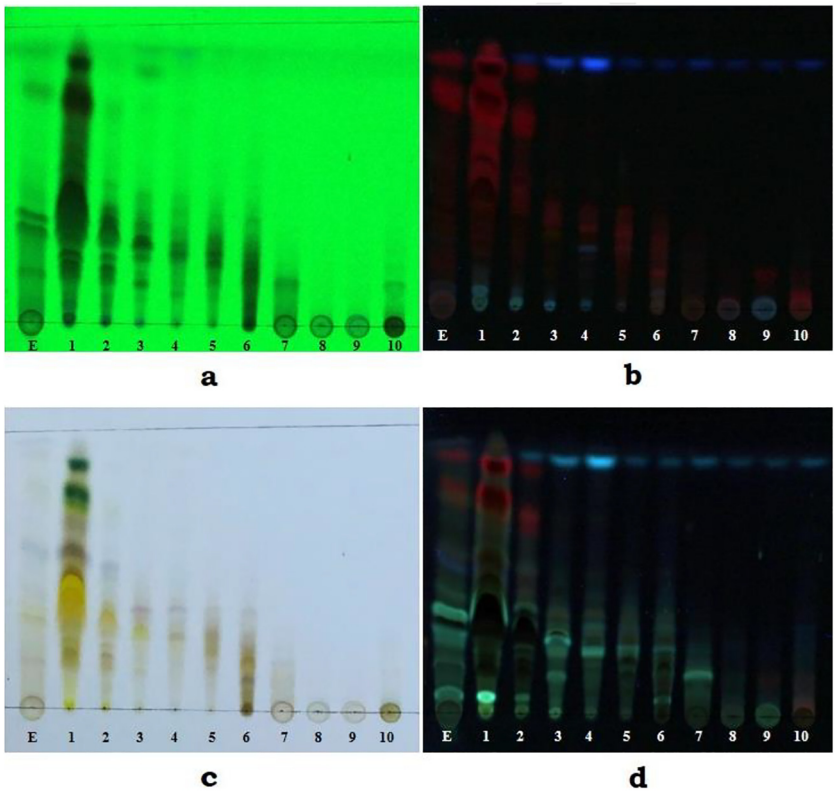

Figure 2: TLC profile of dichloromethane extract (BP12-S-D) and fractions (F1–F10) using silica gel as a stationary phase and chloroform: methanol (98:2 v/v) as a mobile phase. The TLC spots were observed under UV 254 nm (a), UV 366 nm (b), white light after sprayed with H_2SO_4 10% and heated 105 °C for 5 min (c), UV 366 nm after sprayed with H_2SO_4 10%, and heated at 105 °C for 5 min (d).

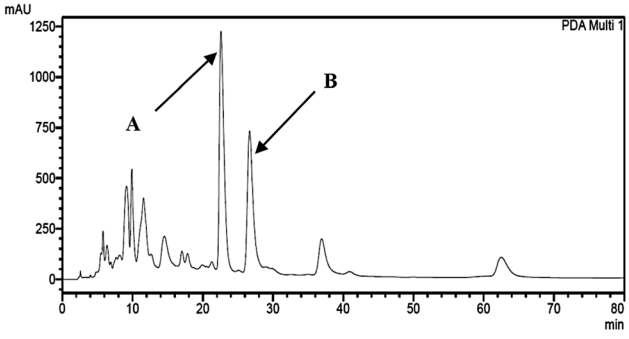

Figure 3: HPLC chromatogram of fraction-1 (F1) with acetonitrile: water (7:3 v/v) mixture as a mobile phase at flow rate 0.5 mL/min, injection volume 40 µL and two major peaks were observed as A and B.

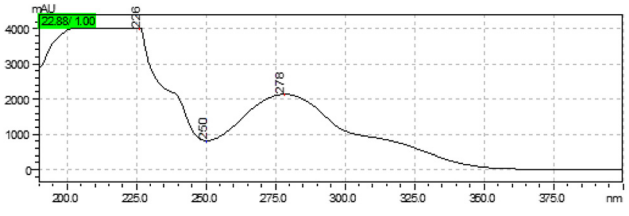

Figure 4: UV–Vis spectra of peak A.

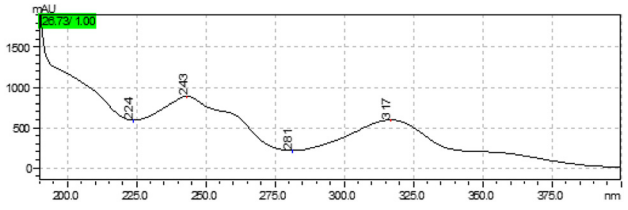

Figure 5: UV–Vis spectra of peak B.

HPLC profile of F1 showed that two major peaks at minute retention times 22.580 (A) and 26.659 (B), which is responsible for its antimalarial activity. Peak A in the UV–Vis spectra has maximum absorption at 226, 250, and 278 nm; it is being expected flavonoid [33]. Meanwhile, peak B has maximum absorption 243, 281, and 317 nm, and it is being expected xanthone [26]. In the future, it is necessary to carry out purification and antimalarial assay on the two peaks to determine which compounds are responsible for antimalarials.

Several studies have been isolated xanthone, flavonoids, phenolics, terpenoids, and steroids from *G. parvifolia*. Parvixanthones A-I, nine new xanthones, isolated from dried bark of *G. parvifolia* [34]. Four novel prenylated depsidones had been isolated from the chloroform soluble

fraction of the leaves of *G. parvifolia* [35]. In fact, flavonoids, terpenoids, xanthones isolated from plants had been reported to contain antimalarial properties. 2,3,4,5,6-pentahydroxyxanthone (X5) inhibits the *in vitro* growth of a chloroquine-sensitive and multidrug-resistant strain of *P. falciparum*. This compound has been shown to have antimalarial action by preventing hemozoin formation [36]. Biflavanones (GB-1) were isolated from the ethanol extract of *Garcinia kola* seed inhibit against *P. falciparum* with IC_{50} values of 0.16 μM and *P. berghei* with ED_{50} values of 100 mg/kg BW [37]. Five xanthones (7-o-methylgarcinone, cowanin, cowanol, cowaxanthone and β-mangostin) from the ethanol bark extract of *Garcinia cowa* were found to possess *in vitro* antimalarial activity against *P. falciparum* with IC_{50} values ranging from 1.50 to 3.00 μg/mL [38]. Likhitwitayamuid et al. (1998) has successfully isolated five xanthones (named 1,7-dihydroxyxanthone; 12b-hydroxy-des-D-garcigerrin A; 1-o-methylsymphoxanthone; symphoxanthone and garciniaxanthone) from *Garcinia dulcis*. These xanthones showed an inhibitory effect on the growth of *P. falciparum* with an IC_{50} value of 0.96–3.88 μg/mL [39]. We hope our study could be continued by isolating the active compound and conducting a toxicity assay. The toxicity assay performed is cytotoxicity to determine the effect in a normal cell using the MTT assay method. This assay was carried out to assess the compound's safety. It could be continued for further research, namely the isolation of active compound because the objective of this research was to obtain an active compound as an antimalarial was proven safe.

Conclusions

This study demonstrated a potential candidate for the new antimalarial drug from dichloromethane extract and fraction of *G. parvifolia* Miq. stem. The fraction-1 (F1) of dichloromethane extract of *G. parvifolia* Miq. stem had the strongest antimalarial activity in LDH assay. F1 showed active antimalarial activity with the IC_{50} value of 6.00 ± 0.03 μg/mL against *P. falciparum* 3D7. The active compounds contained in dichloromethane extract and fraction of *G. parvifolia* Miq. stem are thought to be flavonoids and xanthones.

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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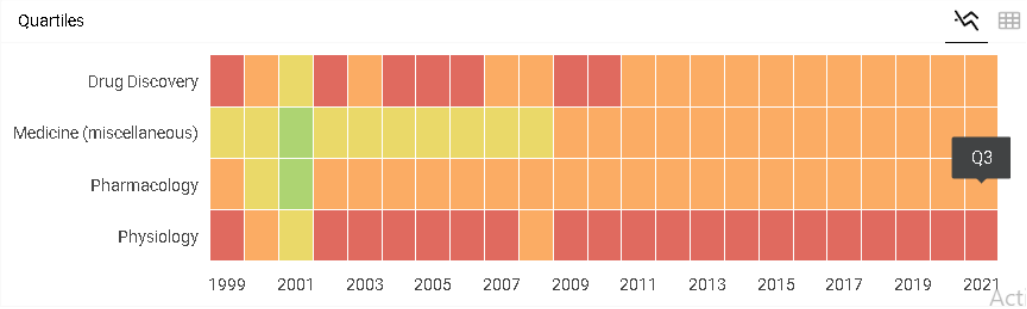

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