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THE POTENTIAL EFFECT OF FLAVONOID FLAVONOL IN STEAMED GYRINOPS VERSTEEGII LEAVES EXTRACT AS ANTIOXIDANTS PREVENTIVE DNA DAMAGES

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ABSTRACT
Gyrinops versteegii is a medicinal plant with high total flavonoid content. This study aimed to analyze the effect water extract of Gyrinops versteegii leaves on DNA damage inhibition in Wistar rats given maximum activity, isolation, identification and testing of antioxidant activity of flavonoid content. solation of flavonoids using maceration method followed by separation, purification and elucidation by spectroscopic method. flavonoid isolates were tested for their antioxidant activity by the DPPH method. Steamed extract of Gyrinops versteggi at doses of 50, 100 and 200 mg/kgBW significantly reduced 8-OHdG levels with an average value from 1.64 ± 0.11, 1.26 ± 0.46, and 1.09 ± 0.17 µmol/mL. this means it can inhibit DNA damage. Identification and structural elucidation of the isolates showed that flavonoid compounds belong to the flavonol group and have strong antioxidant activity with IC50 = 60.7 ppm. Conclusion, the Steamed extract of Gyrinops versteegii leaves has the potentialy to inhibit DNA damage through the mechanism of reducing levels of 8-OHdG and its active flavonoid content as a strong antioxidant.

KEYWORD: Gyrinops versteegii, DNA damage, Flavonol and 8-OhdG.

INTRODUCTION
Flavonol is one of flavonoids aglycones This compound is a natural phenolic compound which is the most abundant in nature, especially medicinal plants, one of the medicinal plants is *Gyrinops versteegii* Compounds of the flavonol group are widely known for their bioactivity as very strong antioxidants such as quercetin (Adi Parwata, et.al., 2018).

As antioxidants, flavonol groups can directly capture free radicals, increase endogenous antioxidants so that they can inhibit oxidative stress which can automatically prevent damage to lipids, proteins and nucleic acids or DNA (Akhlaghi, *et al.*, 2009).

Free radicals *OH and *O2 are the most reactive free radicals in damaging cells. These radicals can directly damage DNA. The mechanism of DNA damage is caused by the reaction of *OH radicals with nitrogenous bases of DNA, namely guanosine so that DNA damage, as described in the following picture (Muraay, 2009),

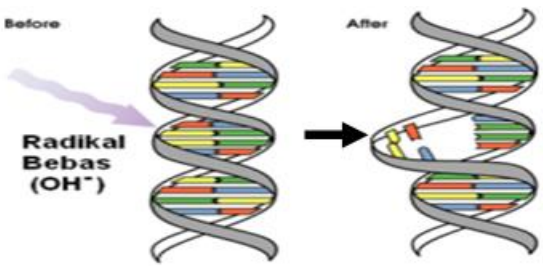


Figure 1. Reaction of *OH with Guanosine.

The oxidation reaction of the OH radical with guanosine will produce 8-hydroxy deoxy guanosine (8-OHdG) as shown in the following reaction, in following figure 2 (Chabowska, 2009; Gupta, 2010).

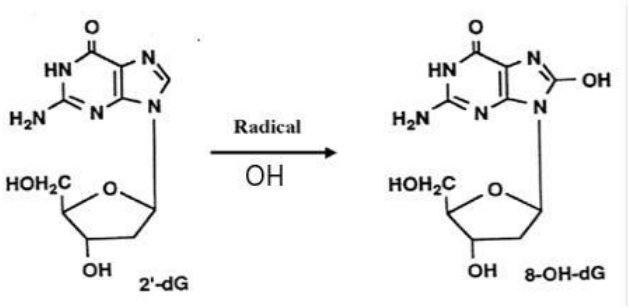


Figure 2. Reaktion Guanosin with *OH.

Gyrinops versteegii plant has been used as a medicine, perfume and incense. Utilization of this because a lot of essential oil content and distinctive smell. Part of the Gyrinops versteegii plant that is used is usually powder rods and resin (results obtained after being injected with mushroom/inoculants). To add to the value of the aloe plant, currently developed Gyrinops versteegii leaves tea as a beverage in the form of Gyrinops versteegii leaves.

In etnomedicine at Singapore, China, Korea, Japan and the United States began to develop Gyrinops versteegii as a remedy for relieving stress, kidney disorders, abdominal pain, asthma, liver cancer, malaria and inflammation stomach. The people of Papua utilizing stem, bark, roots and leaves of Gyrinops versteegii as a malaria drugs (Noviyanti, 2011).

Water extract of Gyrinops versteegii leaves contained phenols, flavonoids, steroids, alkaloids and tannin At the moment public concern for Gyrinops versteegii is the resin produced because it is an expensive export commodity. but the leaves turned out to have a high flavonoid content and have some bioactivity (Adi Parwata, 2018).

Alcoholic extract and steamed leaves of Gyrinops versteegii powder containing secondary metabolites are active as antibacterial, analgesic, anticancer agents and antitukak. Antibacterial test against Escherichia coli showed inhibition of bacterial growth by 11 mm and against Staphylococcus aureus showed bacterial growth inhibition zone was 24 mm, so the potential as an antibacterial. Test against shrimp larvae (BSLT) generate LC50 of 281 ppm so potentially be developed as an anticancer agent because LC50 values <1000 ppm. (Adi Parwata, 2016)

Steamed extract of Gyrinops versteegii leaves significantly increased SOD and Catalase activity in Wistar rats subjected to oxidative stress and antihyperglycemic (Adi Parwata, 2018)

Based on the above background, the researcher wishes to continue research about to analyze in vivo the reduction in 8-OHdG levels of the aqueous extract of Gyrinops versteegii leaves in Wistar rats given maximum activity followed by isolation, identification of flavonoids and their antioxidant activity.

MATERIAL AND METHODS

Material

The leaves plant "Gyrinops versteegii*"* (20 kg) was collected in January, 2020 from Marga, Tabanan, Bali Indonesia. This plant has been identified in the LIPI Botanical Laboratory in the Eka Karya Bali Botanic Garden.

Chemicals and Instruments

Column chromatography techniques with various analytical grade reagents along silica gel (SiO2) were used as a stationary phase. TLC plates (Merck GF-254), 8-OHdG Elisa Kit DNA Damage (Sigma), Wilstatter, Bate Smite-Metcalfe and NaOH 10% reagent, UV-Vis (Jeol HX-110), FTIR (Jasco A-302), spectrophotometer.

Extraction and Fractionation

Gyrinops versteegii was shade dried for a period of 5 weeks and crushed in to coarse powder with the help of mechanical blender. Gyrinops versteegii leaves powder is measured its water content. Its powder extracted with water at a temperature of 80 degrees for about 5 hours. This extract is evaporated with a rotary evapourator. This extract is then used to test the antioxidant activity and isolation of the flavonoids (Biswas R. et.al., 2005).

The extract was again extracted through different solvent system starting from n-hexane followed by chloroform, ethyl acetate so get three fractions i.e. n-hexane, chloroform and ethyl acetate. Each fraction was analyzed for its flavonoids and total flavonoid levels. the fraction that was positive for flavonoids and the highest levels of total flavonoids continued with separation and purification.

Measurement of 8-hydrxy-deoxy guanosin (8-OHdG) levels

Measurement of 8-hydrxy-deoxy guanosin (8-OHdG) was done in vivo analysis. Measurements were carried out in two steps, i.e. the preparation of experimental animals (Wistar rats) and measuring levels of 8-hydroxy-deoxy in the blood of rats under oxidative stress.

Preparation of Wistar rats

Thirty male Wistar rats weighing between 200-250 grams, adapted for 2 weeks then divided into 5 groups (group I, II, III, IV and V). All groups of rats were given maximum activity (swimming). Furthermore group I [C(-

)] was only given aquadest, Groups II, III and IV were given the following treatment : II (T1) was given water extract 50 mg/kgBB, III (T2) was given water extract 100 mg/kgBW, IV (T3) and was given water extract 200 mg/kgBW Group V[C(+)] were given 50 mg/kgBW of Vitamin C (Reagan-Shaw, 2007). After being given the above treatment, the blood was taken. Put into a blood test tube containing EDTA, then centrifuged to take the serum / plasma. Blood plasma was incubated for 24 hours and then 8-OHdG levels were measured by ELISA on a UV-Vis Spectrophotometer.

Measurement of 8-OHdG levels

Measurement of 8-OHdG levels following the procedure of Product Manual 8-OHdG ELISA Kit from Sigma. The units of measurement results is ng/mL.

Separation and Identification Isolat

Separation begins with the determination of the best eluent with TLC GF254 by using several comparisons of eluents with different polarity. This eluent is best used as the mobile phase of column chromatography. The resulting eluent is collected according to the same separation pattern and then evaporated. The eluate analyzed its flavonoids. A positive eluate containing flavonoids was then tested for purity. Flavonoid isolates were identified qualitatively followed identified by UV-Vis spectrophotometer. The isolates were then measured their antioxidant activity using DPPH. Method.

Measurement of Antioxidant Capasity

Measurement begins with the preparation of a standard solution of 0-100 mg/L gallic acid followed by the preparation of a sample solution of steamed extract of Gyrinops verstegii leaves as much as three solutions (3 replicates) The steamed extract was weighed 0.1 gram 3 times, each added with methanol to a volume of 5 mL then vortexed until homogeneous. This solution was centrifuged at 3000 rpm for 15 minutes. Each 0.5 mL solution was pipette then added 3.5 mL 0.1 mM DPPH in methanol in the container and then vortexed. The solution was incubated at 250°C for 30 minutes for the DPPH to react with the sample. The absorbance of each solution was measured at the maximum wavelength = 517 nm (Almey 2010).

Measurement Total Flavonoid Levels

One gram of extract was dissolved in 5 mL of ethanol until homogeneous. Pipette 2.0 mL, put it in a test tube, add 2.0 mL of 2% AlCl3, vortex and then incubate at temperature 29-320C for 25 minutes. This solution was measured at a maximum wavelength of 415 nm. The total flavonoid level was integrated with the calibration curve of the quercetin standard solution. The unit of total flavonoid content is **mg QE/ 100 grams (**Chang and Wen, 2002).

RESULT

Measurement Water Contents of Simplicia

Measurement of water content of Gyrinops verstegi leaves powder simplicia was carried out with three replications. The results obtained respectively 8.9%, 8.58% and 8.59% W/W as shown as Tabel 1, These results indicate the average water contents of Gyrinops versteegii leaves powder, 8,59 ± 0,0058 %W/W. These results are in accordance with the standards set by Materia Medika Indonesia as medicinal raw materials. This simplicia is then used for the manufacture of extracts.

Maceration of 100 grams of sample obtained 400 mL of concentrated extract. This concentrated extract then used for analyze of 8-hidroxy-deoxy Guanosin levels and isolation of the flavonoid compounds.

Measurement of 8-OHdG levels

The results of measuring 8-OHdG levels, explained that steamed water extract of Gyrinops versteegii leaves with doses ranging from 50 to 200 mg/kgBW was able to significantly reduce 8-OHdG levels ($p<0.05$) with an average of 1.65 ± 0.11, 1.28 ± 0.46 and 1.11 ± 0.17 compared to the negative control group without extract with a mean of 1.95 ± 0.61, as described in Table 2 and Figure 3 below,

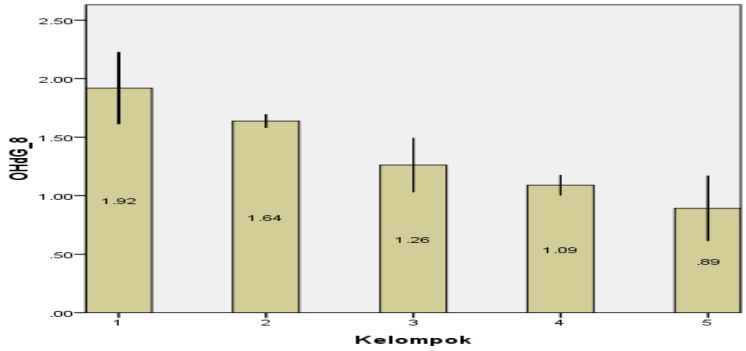
Table 1: Water Contents of Gyrinops versteegii Leaves simplicia.

Code of Sample	Initial weight (g)	Final weight (g)	Water contents (% W/W)
R1	1,1699	1,0694	8,59
R2	1,4630	1,3374	8,58
R3	1,1985	1,0958	8,59
	% Average water contents		8,59

Note : R1: repetition 1; R2: repetition 2; R3: repetition 3

Table 2: 8-OHdG level of Extract.

Group	N	8-OHdG levels (ng/mL)	*F*	p
Without treatment (negative control)	5	1,92±0,61		
Treatment 1 (T1)	5	1,65±0,11		
Treatment II (T2)	5	1,28±0,46	4,62	0,008
Treatment III (T3)	5	1,11±0,17		
Ascorbic acid (positive control)	5	0,89±0,55		



ure 3
The decrease of 8-OHdG Levels

Separation and Identification Isolat

Extracts that actively inhibit DNA damage are further fractionated or partitioned with n-hexane, chloroform and etiasetate. The results of fractionation produced concentrated extract of n-hexane 5.58 grams, chloroform 4.05 grams, and ethyl acetate 8.27 grams. Phytochemical screening with 10% NaOH showed that the fraction of ethyl acetate contained flavonoids and total flavonoid contens 840,12 mg QE /100 grams. Furthermore, isolation and identification of flavonoid compounds were carried out in the ethyl acetate fraction.

Separation by column chromatography begins with eluent selection by using a mixture of several compounds of different polarity and with a certain number of comparisons. Eluent mixture used ethanol: ethyl acetate (2: 8), EtOH: EtAc: n-hexane (5: 4: 1), butanol: EtAc: CH3COOH (2: 7: 1), EtAc : butanol: CH3COOH (5: 3: 2), EtAc: CH3COOH: HCOOH: H2O (10: 1: 1: 2,6). The result of separation by Thin Layer Chromatography obtained eluent ethyl acetate: acetic acid: formic acid: water (10: 1: 1: 2,6) is the best eluent to be used in column chromatograph, as shown in the following table 3,

Table 3: Eluent selection for Coloum Chromatogaphy.

Nu	Eluents type	Number of stain
1.	EtOH : acetic acid (2: 8)	1
2.	EtOH : EtAc : n-hexana (5:4:1)	2
3.	BuOH : EtAc :acetic acid (2:7:1)	1
4.	EtAc : BuOH : acetic acid (5:3:2)	3
5.	EtAc : CH_3COOH : HCOOH : H_2O (10:1:1:2,6)	4

Note : EtOH :ethanol, BuOH : butanol, EtAc : Ethyl acetic

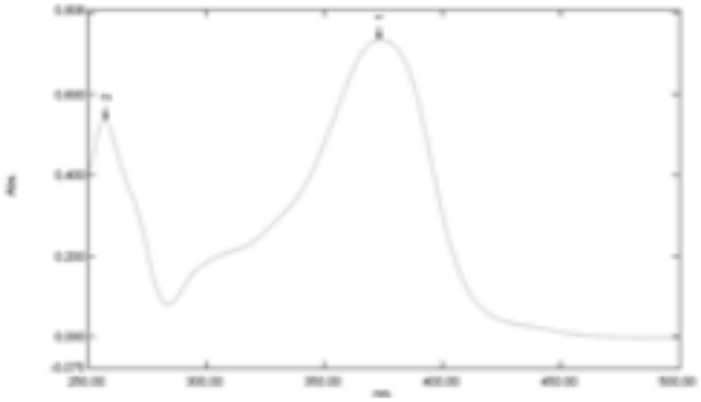
Separation results with column chromatography obtained 4 fractions (A,B,C and D). From these four fractions, it turns out that fraction A with one chromatogram spot and very clear color intensity so that positively contains flavonoids after analyzed with NaOH 10%, Bate-Smith and Wilstatter (Table 4). This fraction was subsequently tested for purity by chromatography. The test results obtained that the pure isolates by thin layer chromatography. These isolates were further identified by UV-Vis and FTIR spectrophotometers.

Table 4: Phytochemical Screening of Fraction A,B,C,D.

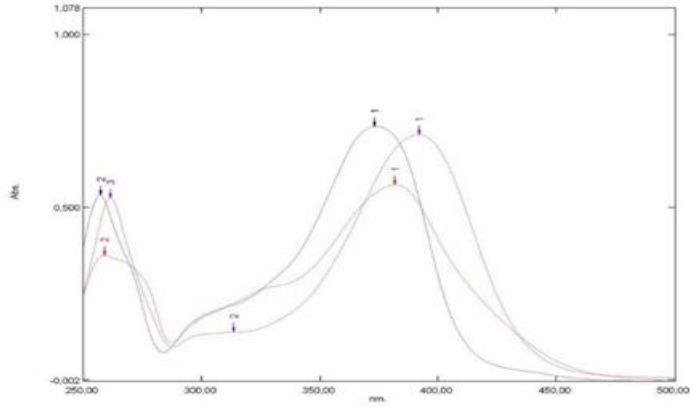
Fraction	Number of spot	Phytochemical Screening	Indicate
A (13-32)	1	+++	Flavonoid
B (33-114)	3	+	Flavonoid
C (115-188)	1	+	Flavonoid
D (189-200)	4	++	Flavonoid

Identification by Ultra Violet-Vicible spectrophotometers

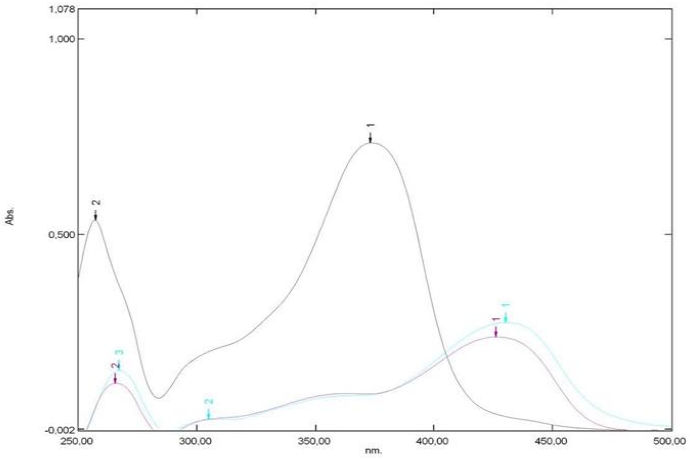
Analysis with a UV-Vis spectrophotometer showing two absorption bands at a maximum wavelength 373,20 nm (band I) and 257,20 nm (band II) as shown in the following figure 3, and than addition of shift reagents NaOAc, NaOAc + H3BO3 and EtOH + AlCl3 there is a shift in bands I and II towards a larger max wavelength (batochromic), while the addition of shift reagent EtOH + AlCl3 + HCl there is a shift towards a smaller max wavelength (hypsochromic) as shown in the following picure 4, 5, 6 and table 5,



Picture 4 Spectra UV-Vis of isolate in Etanol.



Picture 5 Spectra UV-Vis of isolate in Etanol + NaOAc dan H3BO3.



Picture 6 Spectra UV-Vis of isolate in Etanol + AlCl3.

Table 5: Identification isolat structure with UV-Vis Spectrophotometer.

Isolate + shift reagent	λ max (nm)		Shift of λ max (nm)	
	Band I	Band II	Band I	Band II
EtOH	373,20	257,20		
EtOH+NaOAc	381,60	259,00	+8,4	+1,8
EtOH+NaOAc + H_3BO_3	392,00	261,60	+10,4	+2,6
EtOH +$AlCl_3$	430,40	267,40	+ 57,2	+10,2
EtOH +$AlCl_3$ + $AlCl_3$	426,20	265,80	-4,2	-1,6

Identification by FTIR spectrophotometers

Identification of isolates with FTIR spectrophotometer as evidence of the basic functional group in the flavonoid structure of the flavonol group indicated by The peaks that represent the functional group of a compound are clearly depicted in figure 7 and table 6,

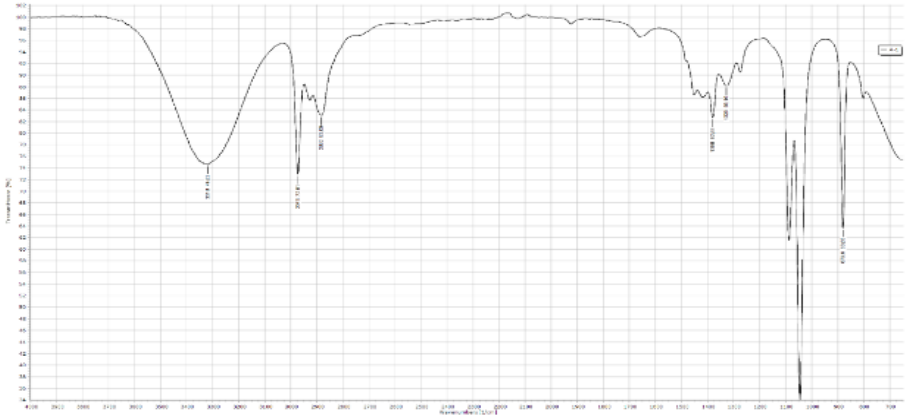


Figure 7. Spectra FTIR of Isolat.

Table 6: Wavenumber of isolates by FTIR spectrophotometer.

No.	Wave number (cm^{-1})	Peaks Intensity	Functional groups Indicated
1	3318	sharp	-OH
3	1100-1000	currently	>C=O
4	1500	currently	>C=C< aromatic
5	1700-1600	currently	-C-O alcohol

Analysis Antioxidant Activity of Isolat

The antioxidant activity of isolates was seen from the value of their antioxidant capacity through the IC50 value. This value was obtained from the linear regression equation between the concentration of isolates vs. % inhibition, IC50 value is the inhibition ability of a substance that can inhibit 50% of the free radical oxidation reaction of DPPH. The IC50 value is obtained from calculations using the linear regression equation y = ax + b). The concentration of the sample is measured by the percent reduction, which is then integrated into the calibration curve. The sample concentration (ppm) as the abscissa (x), while the % attenuation as the ordinate (y). as described in the following table 7 and ficture 7, :

Table 7: Antioxidant capacity of isolate.

Sample	Concentration of Isolat (mg/L)	Absorbance		Linear equations
		blanco	% inhibition	
isolate	20,4	0,529	0,413	y = 0,632x + 11,909 R^2 = 0,9653
	40,8		0,306	
	61,2		0,263	
	81,6		0,2	
IC_{50} (mg/L)			60,27	

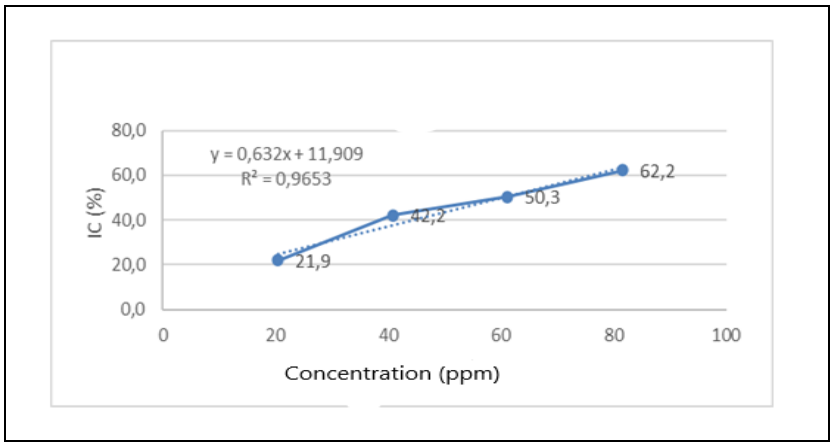
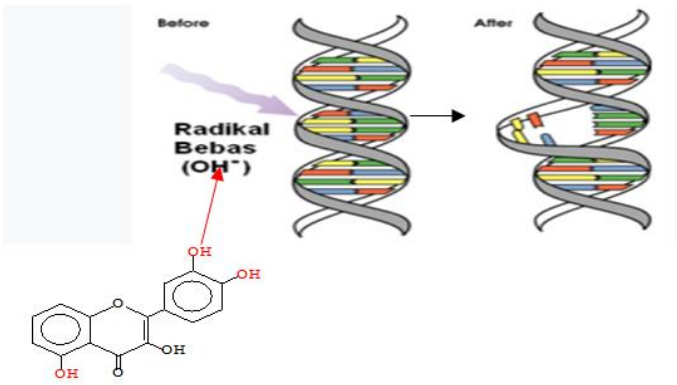


Figure 7: Calibration Graph of Antioxidant Capacity of isolates.

DISCUSSION

The decrease in 8-OHdG levels is due to the flavonoid content of the flavonol group. In this case, flavonoid compounds can directly capture hydroxy free radicals or donate one of their protons to radicals so that the reaction of hydroxy radicals with guanosine does not continue. Due to the discontinuity of the reaction between hydroxy radicals and guanosine, DNA damage can automatically be prevented, as described in the following picture.



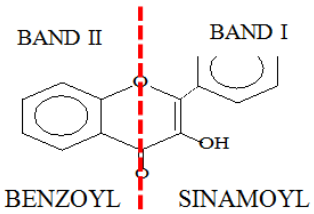
The isolate obtained was in the form of amorphous crystals that were yellow in color and chromatographically pure. This is proven by using Thin Layer Chromatography to produce a single spot.

Based on these results further isolates identified with UV-Vis spectrophotometer with its reagent shift to prove that it is true that the isolate is a flavonoid of the flavonol group and the position of the hydroxy functional groups in rings A, B and C.

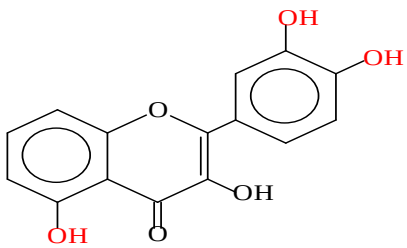
Phytochemical screening using Wilstatter reagent, Bate Smite-Metcalfe and 10% NaOH showed that the isolate was a flavonoid of the flavonol groups.

Analysis with Ultraviolet and Visible spectrophotometer produced two maximum peaks, namely at a maximum wavelength of 257.2 nm and 373.20 nm. This is a characteristic of flavonoids from the flavonol group which produces two absorption bands with maximum wavelengths ranging from 250-280 nm as band II (benzoyl group) and 350-385 nm as band I (cinamoil group) of flavonoids.

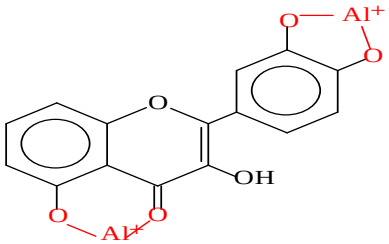
(Markam, 1988) as described in the following picture.



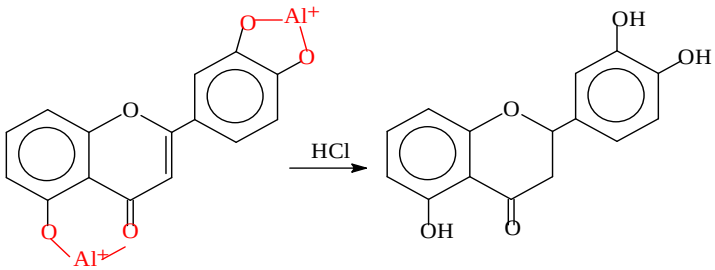
The addition of AlCl3 and HCl shift reagents into the isolate solution in ethanol resulted in a red shift or bathochromic shift. This explains the presence of a hydroxy group on ring B at 3' and 4' and a hydroxy group at number 5 on ring A, as described in the following figure,



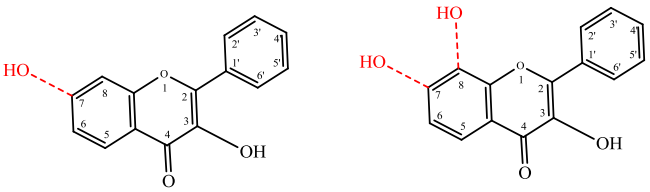
Theoretically it is explained that the addition of AlCl3 to the ethanol isolate solution will form a complex between the hydroxy and carbonyl or hydroxy and hydroxy groups adjacent to Al.as described in the following ficture:

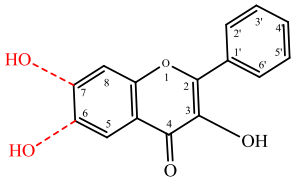


Addition of concentrated HCl solution dropwise into the ethanol isolate solution to which AlCl3 has been added, the Al complex structure will return to its original state and a hypochromic shift occurs as described in the following figure and reaction :

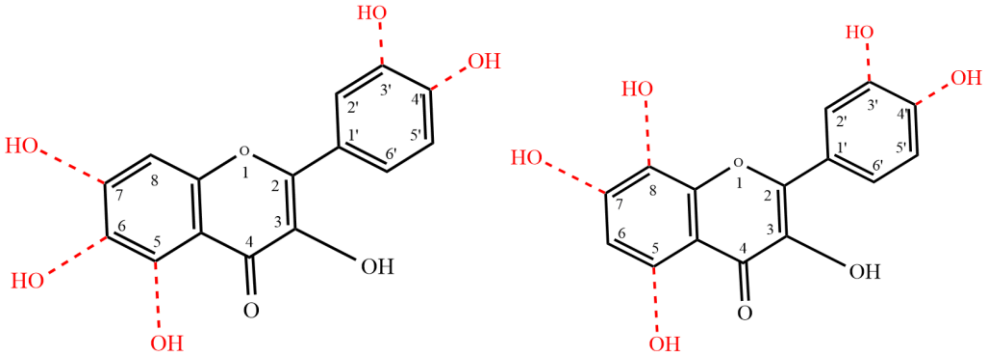


The addition of NaOAc + H3BO3 reagent to isolate fraction A showed a bathochromic shift in band I of 10.4 nm and in band II of 2.6 nm which indicated the possibility of ortho dihydroxy at C6 and C7 or C7 or C8 (Markham, 1988) as described in the following figure:





The addition of shift reagents NaOAc and NaOAc/H3BO3, AlCl3 and AlCl3/HCl indicated that the isolates of fraction A were suspected to be flavonoid compounds belonging to the flavonol group. The flavonoid compounds thought to be present in Girinops versteegii leaves are 5,6,7,3',4' pentahydroxyflavonol or 5,7,8,3',4' pentahydroxyflavonol (Zirconia, 2015), as described in the following figure :



Proof of the existence of basic functional groups in the flavonoid group of flavonols with FTIR spectoscopy showed that it was true that the isolates obtained in this study contained a carbonyl functional group in the ring (> C = O), double bonds in the aromatic ring (> C = C < aromatic), hydroxyl bonded to the ring (-OH) and > C-O.

Measurement of antioxidant capacity of flavonoid isolates showed IC50 = 60.27 ppm. These results explain that the flavonoid isolate of the flavonol group isolated from the water extract of Gyrinops versteegii leaves has strong antioxidant activity.

CONCLUSION

Gyrinops versteegi leaf water extract can inhibit DNA damage through the mechanism of reducing 8-OHdG levels and contains flavonoids of the flavonol group which have strong antioxidant activity.

ACKNOWLEDGEMENT

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Ethical Clearance

The use of Experimental Animals (Wistar Rats) in research has received approval from the Ethics Committee Udayana University, Denpasar, Bali, Indonesia.

Conflict of Interest

This research and writing of this article has no potential conflict of interest to be disclosed.

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