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Sophorae Tonkinensis Radix et Rhizoma

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T cell-associated immunoregulation and antiviral effect of
oxymatrine in hydrodynamic injection HBV mouse model

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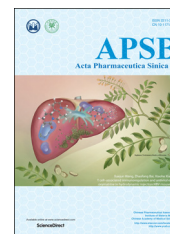
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Graphical Abstracts/Acta Pharmaceutica Sinica B, 7 (2017) iii–vii

Reviews

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Dissecting the role of AMP-activated protein kinase in human diseases

Jin Li^a, Liping Zhong^b, Fengzhong Wang^a, Haibo Zhu^{c,d,e}

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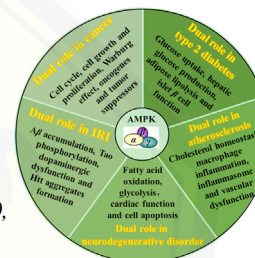
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AMP-activated protein kinase (AMPK) has been identified as an attractive therapeutic target for cancer, type 2 diabetes, atherosclerosis, myocardial ischemia/reperfusion injury and neurodegenerative disease. This review summarizes and updates the paradoxical role of AMPK implicated in these human diseases and put forward the challenge encountered.



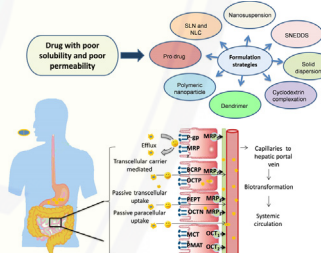
Acta Pharmaceutica Sinica B, 7 (2017) 260

Understanding peroral absorption: regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles

Prachi B. Shekhawat, Varsha B. Pokharkar

Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune 411038, India

Bioavailability of a drug depends on physicochemical properties of the drug and physiological factors and dosage-related factors. Drug absorption occurs from the gut wall by passive diffusion, carrier-mediated uptake and paracellular transport. Several formulation strategies can be used to combat poor bioavailability.



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Nanotechnology-based strategies for treatment of ocular disease

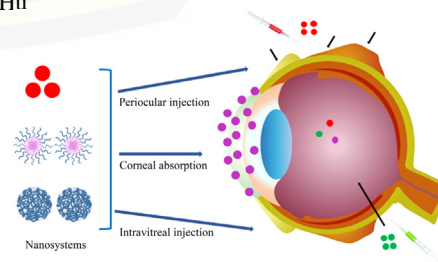
Yuhua Weng^{a,b}, Juan Liu^{b,c}, Shubin Jin^{b,c}, Weisheng Guo^{b,c}, Xingjie Liang^{b,c}, Zhongbo Hu^a

^aCollege of Materials Science and Opto-Electronic Technology, University of Chinese Academy of Sciences, Beijing 100049, China

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In this review, we highlights recent advances in development of nanotechnology-based systems, which could deliver both ocular drugs and gene to the eye via corneal absorption, periocular injection, and intravitreal injection, for ocular disease therapy and diagnosis. Both of nanosystems application and challenge in ophthalmology have been discussed and prospected.

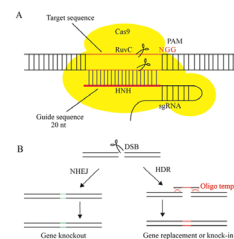


Application of CRISPR/Cas9 in plant biology

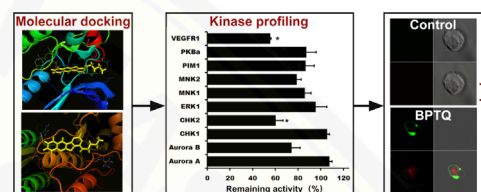
Xuan Liu, Surui Wu, Jiao Xu, Chun Sui, Jianhe Wei

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100193, China

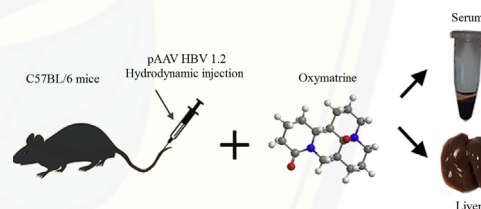
The CRISPR/Cas (clustered regularly interspaced short palindromic repeats/CRISPR-associated proteins) system has received extensive attention owing to its easy manipulation, high efficiency, and wide application in gene mutation and transcriptional regulation in mammals and plants as a revolutionary technology. This review introduces the mechanism of the Type II CRISPR/Cas called CRISPR/Cas9, updates its recent advances in various applications in plants, and discusses its future prospects to provide an argument for its use in the study of medicinal plants.

**Original Articles****Inhibition of protein kinases by anticancer DNA intercalator, 4-butylaminopyrimido[4',5':4,5]thieno(2,3-b)quinoline**Heggodu G. Rohit Kumar^a, Chethan S. Kumar^b, Hulihalli N. Kiran Kumar^a, Gopal M. Advi Rao^a^a*Department of Biochemistry, Davangere University, Shivagangotri, Tholahunase, Davangere 577002, India*^b*SS Institute of Medical Sciences and Research Centre, Inanashankara, Davangere 577005, India*

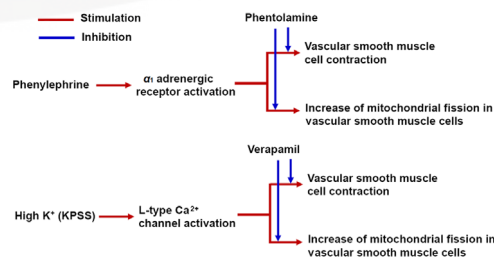
In this study, the ability of pyrimido[4',5':4,5]thieno(2,3-b)quinoline derivatives to interact with different protein kinases was analyzed by molecular docking. 4-Butylaminopyrimido[4',5':4,5]thieno(2,3-b)quinoline (BPTQ) showed a higher order of interaction compared to other derivatives, and effectively inhibited the VEGFR1 and CHK2. BPTQ also induced apoptosis in cancer cells.

**T cell-associated immunoregulation and antiviral effect of oxymatrine in hydrodynamic injection HBV mouse model**Xiuxiu Sang^{a,b}, Ruilin Wang^c, Yanzhong Han^{a,b}, Cong'en Zhang^b, Honghui Shen^b, Zhirui Yang^b, Yin Xiong^e, Huimin Liu^{a,b}, Shijing Liu^c, Ruisheng Li^f, Ruichuang Yang^f, Jiabo Wang^b, Xuejun Wang^d, Zhaofang Bai^b, Xiaohu Xiao^c^a*Chengde Medical College, Chengde 067000, China*^b*China Military Institute of Chinese Medicine, 302 Military Hospital, Beijing 100039, China*^c*Integrative Medical Center, 302 Military Hospital, Beijing 100039, China*^d*Department of Biotechnology, Beijing Institute of Radiation Medicine, Beijing 100850, China*^e*Faculty of Life Science and Technology, Kunming University of Science and Technology, Kunming 650500, China*^f*Research Center for Clinical & Translational Medicine, 302 Military Hospital, Beijing 100039, China*

In the present study, the antiviral effect of oxymatrine (OMT) was investigated in an immunocompetent mouse model. Our findings demonstrate the beneficial effects of OMT on immunologic enhancement and controlling hepatitis B virus (HBV) antigens, offering a good antiviral therapeutic candidate to HBV infection.

**Arterial relaxation is coupled to inhibition of mitochondrial fission in arterial smooth muscle cells: comparison of vasorelaxant effects of verapamil and phentolamine**Jing Jin^{a,b}, Xin Shen^{a,b}, Yu Tai^{a,b}, Shanliang Li^{a,b}, Mingyu Liu^{a,b}, Changlin Zhen^{a,b}, Xiuchen Xuan^{a,b}, Xiyue Zhang^{a,b}, Nan Hu^{a,b}, Xinzi Zhang^{a,b}, Deli Dong^{a,b}^a*Department of Pharmacology (the State-Province Key Laboratories of Biomedicine-Pharmaceutics of China, Key Laboratory of Cardiovascular Research, Ministry of Education), College of Pharmacy, Harbin Medical University, Harbin 150086, China*^b*Translational Medicine Research and Cooperation Center of Northern China, Heilongjiang Academy of Medical Sciences, Harbin Medical University, Harbin 150086, China*

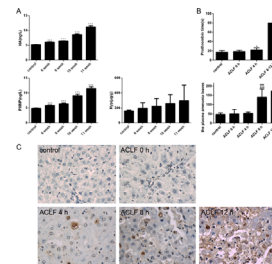
The effects of verapamil and phentolamine in PE- and KPSS-induced vasoconstriction models demonstrated that arterial relaxation was coupled to inhibition of mitochondrial fission in arterial smooth muscle cells.



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Establishment of a new acute-on-chronic liver failure modelFangfang Li^a, Luyang Miao^b, Hua Sun^a, Yuyang Zhang^b, Xiuqi Bao^a, Dan Zhang^a^aState Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China^bShenyang Pharmaceutical University, Shenyang 110016, China

A rat acute-on-chronic liver failure (ACLF) model induced by porcine serum and D-galactosamine/lipopolysaccharide was established and underlying mechanisms of ACLF development were explored.

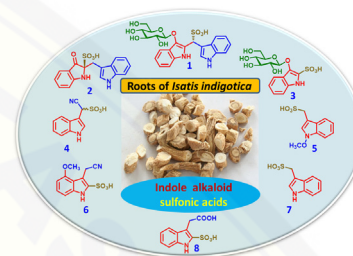


Acta Pharmaceutica Sinica B, 7 (2017) 334

Indole alkaloid sulfonic acids from an aqueous extract of *Isatis indigotica* roots and their antiviral activity

Lingjie Meng, Qinglan Guo, Yufeng Liu, Minghua Chen, Yuhuan Li, Jiandong Jiang, Jiangong Shi

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

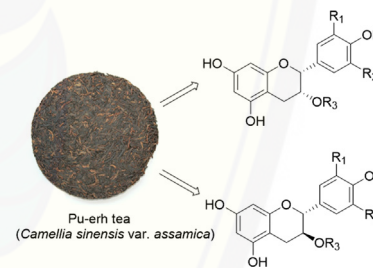
Six new indole alkaloid sulfonic acids (1–6), together with two analogues (7 and 8) that were previously reported as synthetic products, were isolated from an aqueous extract of the *Isatis indigotica* root. Their structures were determined by spectroscopic data analysis, combined with enzyme hydrolysis and comparison of experimental circular dichroism and calculated electronic circular dichroism spectra. In the preliminary assay, compounds 2 and 4 showed antiviral activity against Coxsackie virus B3 and influenza virus A/Hanfang/359/95 (H3N2), respectively.

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Flavanols from the *Camellia sinensis* var. *assamica* and their hypoglycemic and hypolipidemic activities

Xin Wang, Quan Liu, Hongbo Zhu, Hongqing Wang, Jie Kang, Zhufang Shen, Ruoyun Chen

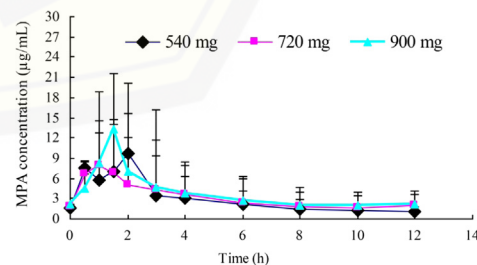
State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

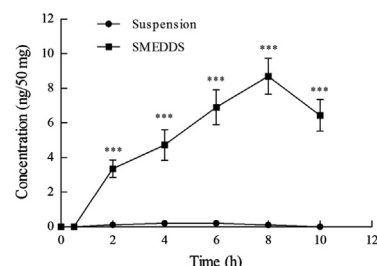
One new flavanol, named (–)-epicatechin-3-*O*-(*Z*)-coumarate (1), and 16 known analogs (2–17) were isolated from the aqueous extract of the pu-erh tea. Compound 15 showed moderate inhibitory effect on sucrose with an IC₅₀ value of 32.5 μmol/L and significant inhibitory effect on maltase *in vitro* with an IC₅₀ value of 1.3 μmol/L; compounds 8, 10, 11 and 15 displayed moderate activity against a lipase with IC₅₀ values of 16.0, 13.6, 19.8, and 13.3 μmol/L, respectively.

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Nonlinear relationship between enteric-coated mycophenolate sodium dose and mycophenolic acid exposure in Han kidney transplantation recipientsJun Zhang^a, Mengmeng Jia^a, Lihua Zuo^a, Na Li^a, Yonggang Luo^b, Zhi Sun^a, Xiaojian Zhang^a, Zhenfeng Zhu^a^aDepartment of Pharmacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China^bDepartment of Integrated Intensive Care Unit, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

This research investigated the pharmacokinetics (PK) of enteric-coated mycophenolate sodium (EC-MPS) by quantification of the active metabolite of mycophenolic acid (MPA) after multiple escalating oral doses in Han kidney transplant recipients. Nonlinear PK properties were discovered at doses ranging from 540 to 900 mg after multiple-dose administration. This may have important contributions to clinical practice.

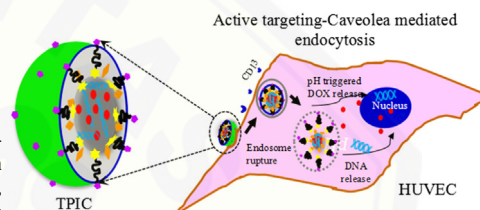
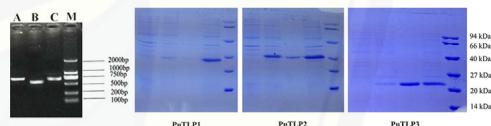


Self-microemulsifying drug delivery system for improving the bioavailability of huperzine A by lymphatic uptakeFang Li^{a,b,c}, Rongfeng Hu^{a,c,d,e}, Bin Wang^{a,c}, Yun Gui^{a,c}, Gang Cheng^{a,c}, Song Gao^{a,c}, Lei Ye^{a,c}, Jihui Tang^f^aAnhui University of Chinese Medicine, Hefei 230038, China^bNational Chinese Medicinal Materials Products Quality Supervision and Inspection Center (Anhui), Bozhou 236800, China^cKey Laboratory of Xin'an Medicine Ministry of Education, Hefei 230038, China^dAnhui "115" Xin'an Traditional Chinese Medical Research & Development Innovation Team, Hefei 230038, China^eAnhui Province Key Laboratory of R&D of Chinese Medicine, Hefei 230038, China^fSchool of Pharmacy, Anhui Medical University, Hefei 230022, China

Compared with the Hup-A suspension, Self-microemulsifying drug delivery system (SMEDDS) formulation can enhance the oral bioavailability and intestinal absorption of Hup-A. According to the detection of Hup-A concentration in mesenteric lymph nodes and the results of the chylomicron flow blocking experiments, Hup-A SMEDDS was confirmed to be absorbed through the lymphatic route.

A preliminary study on the interaction between Asn-Gly-Arg (NGR)-modified multifunctional nanoparticles and vascular epithelial cellsChunxi Liu^a, Tingxian Liu^b, Xiaoyue Yu^b, Yizhu Gu^a^aDepartment of Pharmacy, Qilu Hospital, Shandong University, Ji'nan 250012, China^bSchool of Pharmaceutical Science, Shandong University, Ji'nan 250012, China

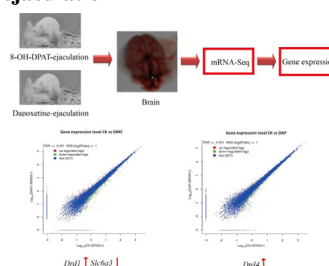
Asn-Gly-Arg (NGR)-functionalized multifunctional poly(ethyleneimine)-poly(ethylene glycol) (PEI-PEG)-based nanoparticles (TPIC) could influence the distribution of CD13 on human umbilical vein endothelial cells through the interaction between CD13 and NGR, causing CD13 clustering, leading to the co-localization of CD13 and caveolin 1, and finally induce the internalization via the caveolea-mediated endocytosis.

**Cloning and expression of three thaumatin-like protein genes from *Polyporus umbellatus***Mengmeng Liu^{a,b}, Dawei Zhang^{a,b}, Yongmei Xing^a, Shunxing Guo^a^aKey Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100193, China^bInstitute of Bioinformatics and Medical Engineering, School of Electrical and Information Engineering, Jiangsu University of Technology, Changzhou 213001, China

For the first time, we have cloned, expressed, and characterized three new PuTLPs from *Polyporus umbellatus*. These PuTLP genes contain N-terminal cleavable signal sequence and are rich in Cys 8–16 residues. Changes in TLP protein levels after *Armillaria mellea* infection in *P. umbellatus* indicated that TLP did play a role in the defense action. The discovery of genes encoding the three TLPs in *P. umbellatus* will shed light on further investigations of defense reactions in *P. umbellatus*. The purified protein with high quality will be the raw material for the production of antibodies to further define the specific function of PuTLPs.

Short Communications**The effect of 8-OH-DPAT and dapoxetine on gene expression in the brain of male rats during ejaculation**Xijun Qin^a, Xiaojun Ma^a, Dongping Tu^a, Zuliang Luo^a, Jie Huang^b, Changming Mo^c^aInstitute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100193, China^bGuangxi University of Chinese Medicine, Nanning 530200, China^cGuangxi Branch of Institute of Medicinal Plant Development, Chinese Academy of Medical Science, Nanning 530023, China

A transcriptomic BodyMap by mRNA-Seq was conducted on the brain at ejaculation of male rats after acute administration of 0.5 mg/kg 8-OH-DPAT or 60 mg/kg dapoxetine (DAP). Compared with the control rats, significant differences in gene expression were observed in the DPAT (349 genes) and the DAP (207 genes). Among them, the expression of *Drd1* and *Slc6a3* was significantly different after treatment with 8-OH-DPAT, whereas that of *Drd4* was significantly different with dapoxetine treatment.

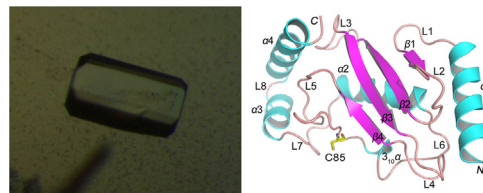


Acta Pharmaceutica Sinica B, 7 (2017) 390**Structural analysis of recombinant human ubiquitin-conjugating enzyme UbcH5c**

Fangshu Wu, Junsheng Zhu, Honglin Li, Lili Zhu

*Shanghai Key Laboratory of New Drug Design, School of Pharmacy,
East China University of Science and Technology, Shanghai 200237, China*

A stable expression system for recombinant UbcH5c was established and one crystal structure of UbcH5c solved at a high resolution. This study provides the basis for further study of UbcH5c including the design of UbcH5c inhibitors.

*Acta Pharmaceutica Sinica B*, 7 (2017) 395**Scanometry as microplate reader for high throughput method based on DPPH dry reagent for antioxidant assay**

Mochammad Amrun Hidayat, Aulia Fitri, Bambang Kuswandi

*Chemo and Biosensor Group, Faculty of Pharmacy, University of Jember,
Jember 68121, Indonesia*

The DPPH solution was immobilized on the microwell plate as dry reagent to construct colorimetric antioxidant sensor. A flatbed scanner was used as a microplate reader to obtain analytical parameters for antioxidant assay as scanometric technique. The sensor was optimized and applied for determining antioxidant capacity of plant extract samples.

*Acta Pharmaceutica Sinica B*, 7 (2017)**Cover story**

Chronic hepatitis B virus (HBV) infection is a heavy health burden worldwide. Immune regulation plays central role in the control of HBV infection. Oxymatrine, extracted from the traditional Chinese anti-viral herb *Sophora tonkinensis* Gagnep, has been shown a remarkable HBV suppressing effect. Current study was investigated in an immunocompetent model of persistent HBV infection which was achieved by liver-targeting manner of hydrodynamic injection of pAAV/HBV1.2. Treatment with oxymatrine accelerated the production of interferon- γ in CD4⁺ T cells and reduced the expression of HBsAg, HBeAg and intrahepatic HBcAg. The immunoregulation and the HBV antigen clearance efficiency of oxymatrine offer a good therapeutic strategy for the treatment of HBV infection.

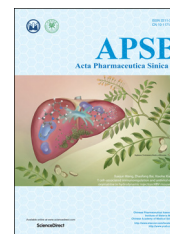
Xuejun Wang, Zhaofang Bai and Xiaohe Xiao



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SHORT COMMUNICATION

Scanometry as microplate reader for high throughput method based on DPPH dry reagent for antioxidant assay



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KEY WORDS

Scanometry;
High throughput;
DPPH;
Optical sensor;
Antioxidant

Abstract The stable chromogenic radical 1,1'-diphenyl-2-picrylhydrazyl (DPPH) solution was immobilized on the microwell plate as dry reagent to construct a simple antioxidant sensor. Then, a regular flatbed scanner was used as microplate reader to obtain analytical parameters for antioxidant assay using one-shot optical sensors as scanometry technique. Variables affecting the acquisition of the images were optimized and the analytical parameters are obtained from an area of the sensing zone inside microwell using the average luminosity of the sensing zone captured as the mean of red, green, and blue (RGB) value using ImageJ[®] program. By using this RGB value as sensor response, it is possible to determine antioxidant capacity in the range 1–25 ppm as gallic acid equivalent (GAE) with the response time of 9 min. The reproducibility of sensor was good (RSD < 1%) with recovery at 93%–96%. The antioxidant sensor was applied to the plant extracts, such as sappan wood and Turmeric Rhizome. The results are good when compared to the same procedure using a UV/Vis spectrophotometer.

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1. Introduction

Antioxidant capacity is a broadly used term as a parameter to characterize different substances and food samples with the ability of scavenging or neutralizing free radicals. This capacity is associated to the presence of compounds capable of protecting a biological system against harmful oxidation¹. There are several synthetic radicals, such as 2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), 1,1'-diphenyl-2-picrylhydrazyl (DPPH), and *N,N*-dimethyl-*p*-phenyldiamine (DMPD), employed for determining antioxidant capacity of various samples²⁻⁵. The DPPH method is one of the most frequently used to assess the ability of compounds as free radical scavengers or hydrogen donors, and to evaluate the antioxidant capacity of food samples. The method was introduced by Blois⁵, and improved by some authors for measuring antioxidant activity of numerous substances and determining antioxidant capacity of various food and plant samples^{3,6,7}. In brief, this method is based on the reduction of the chromogenic DPPH radical by an antioxidant, such as in a plant extract, which causes the radical to change color, and this change can be monitored and quantified using spectrophotometer at 515–520 nm⁸. The radical DPPH is stable and does not have to be generated for hours before the analysis, as in other radical scavenging assays⁹.

In conventional spectrophotometric method, a large volume (1.0–5.0 mL) of freshly prepared DPPH solution in a cuvette is required¹⁰⁻¹⁵. In order to reduce large amount of DPPH solution, a microwell plate can be used in the assay, as it was done by Lee et al.¹⁶. Lately, it was known that no significant different parameters (repeatability, reproducibility, percentage recovery) were observed between microwell and cuvette-based method within intra-laboratory validation⁹. The DPPH microwell-based method is continuously used then by some authors as high throughput screening for antioxidant capacity¹⁷⁻²⁰. To make the assay simpler and faster as high throughput screening, the microwell was used as solid support for DPPH in dry reagent format as described elsewhere¹⁹. By adding methanol or ethanol into the wells, the system can be used for high throughput antioxidant screening of various samples (banana, green tea, pink guava, and honey dew), and it was shown that the results were in good agreement with that of conventional DPPH-microwell platform. However, this method is not suitable for field analysis since specialized, cost-expensive instrument such as microplate reader (spectrophotometer) is required to conduct the assay. To overcome this limitation, flatbed scanner can be used as a microplate reader to obtain digital color image which can be further analyzed quantitatively.

Recently, using scanner as scanometric technique gained its popularity due to its application in various chemical and biochemical assays. The scanometric technique which relies on either a light scattering instrument or flatbed scanner coupled with various probes or sensors can be used for the detection of bacteria, dopamine, magnesium ions, lead ions, thrombin, and mercury ions²¹⁻²⁶. Being subclass of colorimetry, scanometry uses a gray scale as opposed to the various color space. The gray intensity, typically a result of silver enhancement is the measured signal in scanometry²⁷. Scanometry was used to characterize optical feature of various dyes, such as disperse orange 3, methyl orange, fluorescein, eosin Y, rhodamine B, trypan blue, prussian blue, malachite green, methylene blue, chlorophyll b, and DPPH, in a microwell plate²⁸. As the color intensity in red, green, and blue

(RGB) value was mathematically converted to RGB-resolved absorbance, it was shown that flatbed scanner was comparable with spectrophotometer.

Here, we propose a scanometric technique for conducting DPPH assay. In this work, DPPH solution was immobilized on a 96 microwell as dry reagent to construct antioxidant sensor. Then, a regular flatbed scanner was used as microplate reader to evaluate antioxidant capacity of several plant extracts. When it was compared with other DPPH-based sensors^{29,30}, the proposed sensor is simpler, since in other optical sensors the DPPH solution has to be immobilized in polymer (e.g., PVA, PVC) in a long time chemical synthetic reaction to construct the sensor. Moreover, the sensors have to be transferred into a cuvette prior to antioxidant assay in UV/Vis spectrophotometer which made the afore mentioned methods^{29,30} need longer procedure than the proposed method. As regular flatbed scanner was employed for obtaining sensor response, the developed method is extremely cheaper than microplate reader (ELISA reader) or UV/Vis spectrophotometer. In the microplate reader, the absorbance of DPPH after antioxidant addition was measured, while in the proposed scanometric technique, the color intensity (mean RGB) of DPPH after antioxidant addition has been measured for determining antioxidant capacity. Hence, it is obvious that, using scanometric technique, no need the samples to be transparent, as in our previous work¹⁹. In this paper, even non-transparent or opaque sample can be used, since the different analytical response and different instrument were used as a reader for antioxidant sensor response. In addition, we also used less reagent concentration (125 µg/L) compared to the previous one (150 µg/mL)¹⁹. Thus, it make reagent used more efficient, as it is used in one shot measurement. Furthermore, the developed method can be suitable for field analysis and/or in remote area, where medicinal plant extracts can be screened for their antioxidant capacity on site.

2. Materials and methods

2.1. Chemicals

Gallic acid (GA) and DPPH were obtained from Sigma–Aldrich (USA). Methanol was purchased from Merck (Germany). All chemicals were of analytical reagent grade.

2.2. Herbal samples

Herbal samples used in this work, *i.e.*, Sappan wood (*Caesalpinia sappan* L.), and Turmeric Rhizome (*Curcuma domestica* Val.), were purchased from local market of Jember, East Java. All herbal samples were authenticated and deposited at Pharmacognosy Laboratory, Faculty of Pharmacy, University of Jember, Indonesia. Herbal samples were air dried and powdered until their particle size freely passed through sieve 100 mesh.

2.3. Sensor fabrication

Sensor fabrication was done as in our previous work¹⁹ with slight modification. A solution of DPPH in methanol at various concentrations (50, 100, 125, and 150 ppm) were transferred (200 µL) into 96 microwell plate as matrix sensor. The solvent

was then evaporated under mild condition at room temperature to construct antioxidant sensor based on DPPH. Afterward, the antioxidant sensor was ready to be used. For long term used and avoid photodecomposition of DPPH, the antioxidant sensor was sealed with aluminum foil.

2.4. Extraction of herbal samples

All herbal powder were extracted using method reported by Ningsih et al.³¹ with slight modification. The dried herbal powder (10 g) was extracted with methanol (300 mL) for an hour at 30 °C using an ultrasonicator bath (Elmasonic S180H, Germany). The extracts were then filtered through Whatman filter paper No. 1 (USA) by using vacuum funnel. Afterward, the filtrates were separated and stored in well-capped tubes prior to antioxidant assay at room temperature.

2.5. Optimization study

In order to find the optimum DPPH concentration that give best calibration curve in term of linear correlation and the slope, GA was used as standard solution, since it is classified as intermediate based on its antioxidant kinetic, which is more suitable for the optimization study than that of antioxidants with rapid kinetic (ascorbic acid) or slow kinetic (ferulic acid)⁷. GA solution was added in different concentration (1, 5, 10, 15, 20, and 25 ppm) to each well 150 μ L of methanol and 50 μ L of GA solution were added. After 9 min, the color change of each well was quantified using the measurement procedure, where the calibration curve can be constructed.

2.6. Measurement procedure

The color change of sensor was captured using flatbed scanner (Canoscan, LIDE 110, Japan) in which color photo mode with resolution at 300 dpi was set for image scanning. The color intensity was then analyzed with ImageJ[®] program for Windows[®]. The color intensity of sensors (Δ RGB) was obtained by subtracting the intensity value of mean RGB of the application of sample from the intensity value of mean RGB without the sample. All of the experiments were carried out in triplicate measurements.

3. Results and discussion

3.1. The antioxidant sensor

The fabrication of antioxidant sensor based on DPPH was performed by surface coating on the bottom of the 96 microwell plate with the 200 μ L DPPH solution (125 ppm) as it can be seen in our previous work¹⁹. The process was very simple, by just evaporate the DPPH solvent in 40 min, then leaving DPPH dry reagent as immobilized reagent on the bottom of each well. After this immobilization process, the antioxidant sensor was ready to be used as antioxidant sensor.

3.2. Sensing scheme

In this sensing scheme, DPPH as radicals is used as the basis for optical detection in the assessment of antioxidant activity⁵⁻⁷. This

is due to the fact that DPPH has been widely used for the determination of antioxidant activity of phytochemicals, such as flavonoids and polyphenols^{18,19}. In this assay, the purple of chromogen radical (DPPH[•]) is reduced by antioxidant (*e.g.*, GA) to the corresponding pale yellow hydrazine (DPPH-H). Reduction of the chromogenic purple radical (DPPH[•]) by hydrogen-donating antioxidant is monitored by capturing its color change to the pale yellow of the antioxidant sensor. The sensing mechanism is shown in Fig. 1, where AH is donor molecule, and A[•] is free radical produced.

This DPPH as chromogenic radical reagent was chosen, since it is widely used in well-established procedures for the antioxidants assay, together with sufficient chemical stability in a dry reagent format, avoiding problems associated with leaching¹⁹, as it will dissolve again when sample introduced. In addition, there is no need for regeneration of radicals *in situ*, which makes the antioxidant sensor simpler and more practical.

3.3. Optimization of DPPH concentration

The antioxidant sensor works as the color change from purple to yellow by introducing antioxidant such as GA; therefore, the optimum color change of the sensor would be depend on the DPPH concentration. In order to optimize the DPPH concentration in term of its calibration curve, various concentration of DPPH have been immobilized as antioxidant sensor and tested toward the increased concentration of GA (1–25 ppm). After scanometric measurements, the calibration curves of GA *vs.* color intensity (Δ RGB) were made for each DPPH concentration (50, 100, 125 and 150 ppm) tested as given in Table 1. The antioxidant sensor with 125 ppm DPPH was selected as optimum DPPH concentration in term of its linear correlation and slope. The slope and coefficient correlations (*r*) of the 125 ppm DPPH have been found to

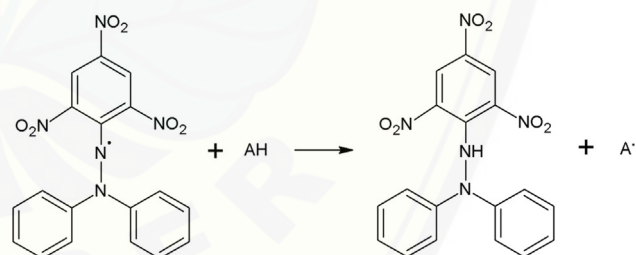


Figure 1 The reaction mechanism of DPPH radical with antioxidant (AH).

Table 1 The calibration curves of gallic acid (1, 5, 10, 15, 20, and 25 ppm) towards various DPPH concentrations for the antioxidant sensor (*n*=3).

DPPH conc. (ppm)	<i>r</i> ²	Equation of calibration curve	Slope
50	0.9873	$y = 3.2809x + 0.4224$	3.2809
100	0.9911	$y = 3.3118x - 1.1945$	3.3118
125	0.9922	$y = 3.4257x - 3.3301$	3.4257
150	0.9912	$y = 3.2353x - 1.3858$	3.2353

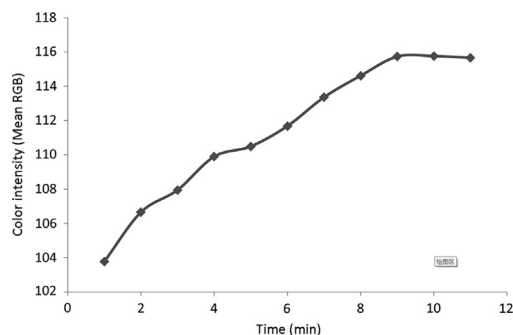


Figure 2 Response time of the antioxidant sensor towards gallic acid (15 ppm).

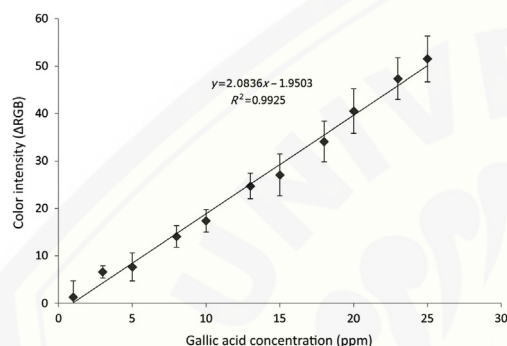


Figure 3 Sensor response towards gallic acid (1–28 ppm), $n=3$.

be 3.426 and 0.996, respectively, which is higher compared to other DPPH concentrations (50, 100 and 150 ppm) as it can be seen in Table 1. Therefore, the antioxidant sensor with DPPH concentration of 125 ppm was used for further measurements.

3.4. Response time

The response time of antioxidant sensor was investigated using 15 ppm GA solution. The response of sensor was recorded at every 2 min until stable color intensity value was obtained. The response time of sensor was observed at 9 min. After this period, the sensor gave stable response as shown in Fig. 2. Therefore, this response times was used for further measurements.

It can be seen in Fig. 2 that the developed sensor has response time at 9 min which is faster than that of other DPPH-based optical sensor³⁰, while the similar GA concentration was applied (± 1 mmol/L). Moreover, our sensor takes a short operating time in the term of time of analysis, while DPPH absorbance was typically read at 30 min after addition of tested samples in other microwell-based methods^{18,19}. Similar time of analysis (10 min) was also reported with observed in other microwell-based method²⁰; however, the method was suffered from co-solvent and/or buffer addition. Hence, it can be drawn that our developed method is simpler and faster than afore mentioned methods.

3.5. Antioxidant determination

GA was used as standard for antioxidant assay in this work. The calibration curve was constructed by plotting concentration of GA

Table 2 The antioxidant sensor response towards 10 ppm of gallic acid ($n=6$).

Sample	RGB	Δ RGB
Blank	43.62	–
1	71.724	28.104
2	70.814	27.194
3	71.237	27.617
4	71.603	27.983
5	71.712	28.092
6	71.301	27.681
Mean		27.779
RSD (%)		1.271

vs. sensor response as Δ RGB value as depicted in Fig. 3. It can be seen that the linear range of the sensor response is in the range of 1–25 ppm with the coefficient correlation (r) of 0.996. The detection limit (LOD) of the antioxidant sensor, which is defined as the concentration of sample yielding a signal equal to the blank signal plus three times of its standard deviation³², was calculated to be 0.762 ppm. The reproducibility of the sensor response was tested toward 10 ppm of GA solution as given in Table 2, the precision of sensor can be observed. It can be seen that RSD value was lower than 2%, indicating the developed method has good precision³².

3.6. Recovery

The percentage recovery values for the accuracy of the sensor on the determination of antioxidant activity are performed by adding 30%, 45% and 60% to initial 12, 13, and 15 ppm of GA in sample simulation. The mean of percentage recovery (%) was calculated to be 91%–96% as it can be seen in Table 3. This results were in good agreement with theoretical recovery values (%) for unit concentration of 10 ppm (80%–110%)³³. Therefore, the developed method indicated a good accuracy for antioxidant measurements.

3.7. Sensor stability

In this work, various storage conditions were applied for stability test of the developed sensor. The sensor was stored separately in a well-capped cabinet at room (30 °C) and chiller (4 °C) temperature. Then, the sensor response towards GA (1–25 ppm) was

Table 3 Recovery study of gallic acid (%) in simulated sample using the antioxidant sensor ($n=3$).

Sample	Found concentration (ppm)	Recovery (%)
Initial (10 ppm)	10.135 \pm 0.008	101.350 \pm 0.084
30% addition	2.546 \pm 0.075	83.747 \pm 2.397
45% addition	4.417 \pm 0.063	96.840 \pm 1.462
60% addition	6.115 \pm 0.365	100.551 \pm 5.924

observed in every week, until 10% decrease of initial response was obtained. After two weeks, sensor response was observed to decrease more than 10% when sensor was stored at room temperature as it can be seen in Table 4. Hence, it can be noted that stability of sensor was only maintained during one week storage at room temperature. This finding seemed to be found in other DPPH-based optical sensor, in which the absorbance of DPPH-polymer film was completely loss within one week storage at room temperature³⁰.

Table 4 The decrease of sensor response towards gallic acid (1–25 ppm) after it was stored in room temperature (30 °C).

Gallic acid conc. (ppm)	Storage time (week)				
	1	2	3	4	5
1	9.16	12.93	15.45	17.22	19.14
5	2.19	11.02	13.34	13.50	14.59
13	7.34	12.68	13.89	15.83	44.21
25	3.46	12.53	11.85	12.02	15.02

In order to obtain the stable sensor response, the sensor was also stored in chiller temperature right after fabrication step as it was described earlier. Table 5 shows that sensor response towards GA (1–25 ppm) was found to be stable during six-week storage at chiller temperature. After six week, the sensor response was decreased more than 10% (data not shown), suggesting that stability of sensor

Table 5 The decrease of sensor response towards gallic acid (1–25 ppm) after it was stored in chiller temperature (4 °C).

Gallic acid conc. (ppm)	Storage time (week)					
	1	2	3	4	5	6
1	0.81	1.40	2.33	3.21	7.45	7.67
5	3.12	3.67	3.68	3.92	4.87	5.29
13	4.80	6.07	6.40	7.26	7.43	8.22
25	1.50	2.61	2.83	4.69	7.12	7.49

Table 6 The comparison results of antioxidant capacity (ppm GAE) of various plant extracts determined by the antioxidant sensor and the UV/Vis spectrophotometer ($n=3$, $\alpha=0.05$).

Sample extracts	Antioxidant sensor-scanometric	UV/Vis Spectrophotometer	Significance value (<i>P</i>)
Sappan wood (10%, w/v)	10.22 ± 0.07	10.55 ± 0.21	0.062
Turmeric Rhizome (0.1%, w/v)	10.72 ± 0.26	11.08 ± 0.09	0.082

was only preserved during six week storage at chiller temperature.

3.8. Application on plant extracts

In order to demonstrate the practical used of scanometry, various plant extract, such as sappan wood and Turmeric Rhizome, were carried out. Here, Sappan Lignum and Turmeric Rhizome were used with some purposes. Firstly, they were used to show that the color of herbal extracts did not affect the measurement of antioxidant capacity (the color of sappan extract is red, while the color of turmeric is yellow), and that the sensing mechanism relied on redox activity only. Secondly, the sample is taken based on the part of plant organ used for medication, e.g., sappan is represented woods, while turmeric is represented rhizome. Thus, the proposed antioxidant sensor can be used for determination of antioxidant activity in any part of plant organ (leaf, root, flower, etc.) extracts or other plants extracts.

In this work, antioxidant capacity of plant extracts were compared with that of GA, as this approach was also reported in some literatures^{34–37}. Using calibration curve of GA (5–25 ppm) made by the scanometric technique, the antioxidant capacity of extract was calculated, as it was expressed as gallic acid equivalent in ppm (ppm GAE). As comparison, UV/Vis spectrophotometry was used for the assay of antioxidant capacity of sample plant extracts with absorbance reading at 515 nm. Then, the results based on the scanometry were compared with the assay using UV/Vis spectrophotometer. The results showed that the proposed method was in good agreement with the spectrophotometric method, as it can be seen in Table 6, indicating the feasibility of the proposed scanometry for the determination of antioxidant capacity of the plant extracts.

4. Conclusion

A scanometry has been used as a microplate reader for high throughput screening of antioxidant based on DPPH as dry reagent on microwell plate as also used by other²⁸. However, the proposed method is the first application for antioxidant sensor, measuring antioxidant capacity of GA and plant extracts. In this work, the developed method has linear range at 1–28 ppm with LOD at 0.794 ppm, and it was found to be reproducible, and good recovery for antioxidant determination of several plant extracts. The used of scanner in this proposed method is simple, easy to

operate, and low-cost, as well as it can be used as an alternative reader for the microwell plate.

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